FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM (PCNS) DRUGS ADVISORY COMMITTEE MEETING

Wednesday, May 22, 2013

8:00 a.m. to 5:00 p.m.

FDA White Oak Campus

Building 31, The Great Room (Room 1503)

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Glendolynn S. Johnson, Pharm.D.

Division of Advisory Committee & Consultant Management

Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Emilia Bagiella, Ph.D.

Professor of Biostatistics

Department of Health Evidence and Policy

Mount Sinai School of Medicine

New York, New York

Robert R. Clancy, M.D.

Professor of Neurology and Pediatrics

The University of Pennsylvania School of Medicine

Division of Neurology

The Children's Hospital of Philadelphia

Philadelphia, Pennsylvania

Jeffrey A. Cohen, M.D.

Professor, Neurology

Dartmouth Medical School

Section Chief, Neurology

Director, Clinical Neurophysiology Fellowship

Dartmouth Hitchcock Medical Center

Lebanon, New Hampshire

Richard P. Hoffman, Pharm.D.

(Consumer Representative)

Hernando, Florida

Michelle M. Mielke, Ph.D.

Associate Professor

Division of Epidemiology

Department of Health Sciences Research

Mayo Clinic

Rochester, Minnesota

Paul B. Rosenberg, M.D.

(Acting Chairperson)

Associate Professor of Psychiatry and Behavioral Sciences

Division of Geriatric Psychiatry and Neuropsychiatry

John Hopkins University School of Medicine

Baltimore, Maryland

Jason W. Todd, M.D.

Staff Neurologist

NorthEast Neurology

Concord, North Carolina

Justin A. Zivin, M.D.

Professor Emeritus

University of California San Diego

La Jolla, California

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEMBER (Non-Voting)

Lynn Kramer, M.D., FAAN ***(Industry Representative)***

President, Neuroscience PCU

Eisai, Inc.

Wood Cliff Lake, New Jersey

TEMPORARY MEMBERS (Voting)

Ronald D. Chervin, M.D., M.S.

Professor of Neurology

Michael S. Aldrich Collegiate Professor of Sleep Medicine

Director, Sleep Disorders Center

University of Michigan

Ann Arbor, Michigan

Natalie Compagni Portis, Psy.D.

(Patient Representative)

Oakland, California

Christian Guilleminault, D.M., M.D., DBiol
Professor, Stanford University School of Medicine
Sleep Medicine Division
Stanford, California

Daniel G. Morrow, Ph.D.
Professor, Department of Educational Psychology
University of Illinois at Champaign-Urbana
Champaign, Illinois

Matthew Rizzo, M.D., F.A.A.N.
Professor of Neurology, Mechanical and Industrial Engineering, and Public Policy
Director, University of Iowa Aging Mind and Brain Initiative
Vice Chair for Translational and Clinical Research & Director, Division of Neuroergonomics
Department of Neurology
Roy & Lucille Carver College of Medicine
University of Iowa
Iowa City, Iowa

Roger R. Rosa, Ph.D.

Deputy Associate Director for Science

Office of the Director

National Institute for Occupational Safety & Health

Centers for Disease Control and Prevention

Washington, District of Columbia

TEMPORARY MEMBERS (Voting)

Richard J. Ross, M.D., Ph.D.

Staff Physician

Philadelphia Veterans Affairs (VA) Medical Center

Professor of Psychiatry at the Philadelphia VA

Medical Center

Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Lisa M. Schwartz, M.D., M.S.

Professor, Medicine and Community and Family Medicine

Geisel School of Medicine at Dartmouth

Co-Director, Center for Medicine and the Media

The Dartmouth Institute for Health Policy and Clinical Practice

Director, VA Outcomes Group, VA Medical Center

White River Junction, Vermont

Robert B. Voas, Ph.D.

Senior Research Scientist

Pacific Institute for Research and Evaluation

Beltsville, Maryland

FDA PARTICIPANTS (Non-Voting)

Ellis Unger, M.D.

Director, Office of Drug Evaluation I (ODE-I)

Office of New Drugs (OND), CDER, FDA

Ronald Farkas, M.D., Ph.D.

Clinical Team Leader, DNP

ODE-I, OND, CDER, FDA

Russell G. Katz, M.D.

Director, Division of Neurology Products (DNP)

ODE-I, OND, CDER, FDA

Hristina Dimova, Ph.D.

Sr. Clinical Pharmacology Reviewer

Division of Clinical Pharmacology I (DCP-I)

Office of Clinical Pharmacology (OCP)

Office of Translational Sciences (OTS)

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ROSENBERG: Good morning. My name is Paul Rosenberg. I would first like to remind everyone to please silence your cell phones, smart phones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Chris Kelly.

Chris, if you are here, please stand.

I'd like to ask all the members, consultants, FDA panel, and DFO to go around the table and state their name into the record. My name is Paul Rosenberg. I'm associate professor of psychiatry at Johns Hopkins. I specialize in trials of Alzheimer's disease.

Dr. Unger, we'll start at your end.

DR. UNGER: I'm Ellis Unger. I'm the director of Office of Drug Evaluation I in the Office of New Drugs at CDER, FDA.

DR. KATZ: Rusty Katz, the director of

Division of Neurology Products, FDA.

DR. FARKAS: Ron Farkas, clinical team leader, Division of Neurology Products at FDA.

DR. DIMOVA: Hristina Dimova, clinical pharmacology reviewer, FDA.

DR. MORROW: I'm Dan Morrow, professor of educational psychology, University of Illinois.

DR. SCHWARTZ: Lisa Schwartz, professor of medicine at Dartmouth Medical School.

DR. ZIVIN: Justin Zivin. I recently retired from the neurosciences department at UCSD Medical School, and my fundamental interest in research has been stroke.

DR. TODD: Jason Todd. I'm a neurologist with Carolinas HealthCare System. I practice general neurology with a focus on sleep.

DR. MIELKE: Michelle Mielke. I'm an associate professor of epidemiology at the Mayo Clinic.

DR. VOAS: Bob Voas. I'm with the Pacific Institute for Research and Evaluation in Maryland, formerly with the National Highway Traffic Safety

Administration.

DR. ROSENBERG: Paul Rosenberg from Johns Hopkins. I'm an associate professor of psychiatry.

DR. JOHNSON: Good morning. Glendolynn Johnson, designated officer for the PCNS committee.

DR. CLANCY: I'm Robert Clancy, professor of neurology and pediatrics at the University of Pennsylvania School of Medicine.

DR. HOFFMAN: I'm Richard Hoffman. I'm a pharmacist and medical writer, and I'm the consumer representative for this committee.

DR. PORTIS: I'm Natalie Compagni Portis. I'm a psychologist, and I'm the patient representative in the meeting today.

DR. BAGIELLA: Emilia Bagiella. I'm a professor of Biostatistics at Mount Sinai School of Medicine.

DR. CHERVIN: My name is Ron Chervin, and I direct the Sleep Disorders Center at the University of Michigan.

DR. GUILLEMINAULT: Christian Guilleminault, Division of Sleep Medicine, Stanford University

Medical School.

DR. RIZZO: I'm Matt Rizzo. I'm a professor of neurology, mechanical and industrial engineering, and public policy at the University of Iowa.

DR. ROSA: Roger Rosa. I'm deputy associate director for science at the National Institute for Occupational Safety and Health.

DR. ROSS: I'm Richard Ross, professor of psychiatry at the Philadelphia VA Medical Center and the Perelman School of Medicine at the University of Pennsylvania.

DR. COHEN: Jeffrey Cohen, professor and now, unfortunately, interim chairman of neurology at Dartmouth Medical School.

DR. KRAMER: Lynn Kramer. I'm a neurologist and the industry representative on this panel.

DR. ROSENBERG: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which will be strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of

these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it to Lieutenant Commander Glendolynn Johnson, who will read the conflict of

interest statement.

Conflict of Interest Statement

DR. JOHNSON: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC Section 208 is being provided to the participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of

interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts of interest when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions at today's meeting, members and temporary members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application 204569 for suvorexant tablets, submitted by Merck Sharp and Dohme Corporation for the proposed indication of insomnia characterized

by difficulties with sleep onset and/or maintenance.

This is a particular matters meeting, during which specific matters related to Merck suvorexant will be discussed. Based on the agenda and all financial interests reported by the committee members and temporary members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Lynn Kramer is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Kramer's role at this meeting is to represent industry in general and not any particular company. Dr. Kramer is employed by Eisai.

We would like to remind members and

temporary members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firms at issue. Thank you.

DR. ROSENBERG: We will now proceed with Dr. Katz's introductory remarks.

FDA Introductory Remarks - Russell Katz

DR. KATZ: Thanks, Dr. Rosenberg. I'd like to add my welcome to the committee members today, and in particular to the invited guests that we've asked to come to add their expertise to the committee and the discussion. So thanks very much, everybody, for coming.

My goal here is to give a very brief overview of what we think are the main issues that we would like the committee to discuss. You know

that we have a detailed list of discussion topics and some actual voting questions, and they go through all the specifics, and we want all those covered as well. But I just want to give you a very brief, overarching view of what we think the main issues are.

So today, as you know, we'll be considering NDA 204569 submitted by Merck Sharp and Dohme for the use of suvorexant in the treatment of insomnia characterized by difficulty falling asleep and/or difficulty staying asleep. Suvorexant is the first of a new class of orexin antagonists, and so it's an exciting compound to be discussing and have the opportunity to review.

In support of the application, the sponsors submitted the results of two phase 3 controlled trials, each of which compared two doses, two fixed doses, to placebo, as well as a smaller phase 2 crossover trial, study 006 that compared several different fixed doses to placebo.

In the phase 3 studies, as I'm sure you know, patients were dosed according to their age so

that patients under 65 years of age were randomized to receive either 20 or 40 milligrams at night or placebo, and patients 65 and over received either 15 or 30 milligrams at bedtime or placebo.

Presumably, the difference in doses was based on kinetic considerations and also potentially pharmacodynamic considerations, given that in general, it's been presumed that older people are more sensitive to these drugs, although there's some evidence in the application that that's not the case, at least for some outcomes. And I think we'll cover that.

In the studies that were submitted, patients were assessed by both subjective and objective measures -- objective measures as assessed through polysomnography -- of both sleep onset and sleep maintenance problems; this is typical of studies of hypnotics, the objective measure we take to be the truth about how long it took people to be able to fall asleep or to stay asleep.

The subjective measures are typically designed to assess whether or not any changes that

were seen on objective measures really were clinically meaningful to the patient. Whether or not the subjective measures that we use typically and that were used here actually get at that question is something we may want to discuss. But nonetheless, this is a standard approach to assessing the effects of hypnotic drugs.

The subjective measure of sleep latency was time to sleep onset. Objectively, that's measured as what's called latency to persistent sleep. The sleep maintenance issues are assessed subjectively with total sleep time, and objectively with wake time after sleep onset, or WASO. Again, these are standard measures. These phase 3 studies were 3 months long; that's more or less a standard duration of treatment in these studies.

The phase 2 two-period crossover study examined fixed doses of 10, 20, 40, and 80 milligrams and placebo, each of which was given for 4 weeks. This was a two-period counterbalanced crossover. The primary outcome in that study was sleep efficiency, which was defined as the total

sleep time divided by the time in bed, in minutes, times 100. But in addition, this study also looked at objective measures of latency and sleep maintenance.

The sponsor also of course has included extensive safety analyses, including, critically -- and we'll hear a lot about this today, I'm sure -- two well-conducted studies of driving behavior, one in the elderly and one in the non-elderly. And in those studies, the doses to which patients were randomized were the same doses to which those populations were randomized in the phase 3 studies, 15 and 30 for the elderly and 20 and 40 for the non-elderly.

It's very important to recognize at the outset that our view is -- and especially for hypnotic drugs, which generally are excepted to have and do have residual next-day effects that can be of great concern -- that labeling recommend that the lowest effective dose be the dose that patients get initiated on treatment -- for the obvious reasons. You want to minimize the next-day

effects, if you can, if you can get away with a low dose -- and that higher doses should really only be recommended if the lower doses prove ineffective. We think that insomnia is a condition that lends itself to this sort of dosing recommendation. We think it's important, and this is a concept that we have recently embodied in some labeling changes for other hypnotic drugs, and we believe this is the right way to go.

We believe this even if the lowest dose is shown or believed to be not quite as effective as the higher doses. But if it's effective at all, we think that's the way the labeling should be written. And in fact, the sponsor is proposing now that labeling is in conformity with that principle, so that the first dose in non-elderly -- for example, they propose it should be 15 milligrams, and only if that's really not effective, the higher dose of 30 in that population should be recommended.

Let me just say at the beginning that in our view, the data taken as a whole establish that

suvorexant does have effects, is effective for sleep latency and sleep maintenance. But again, to keep faith with the principle of recommending the lowest effective dose, at least initially in patients, it's very important for us to look at the data for all doses that have been studied and determine whether or not any doses that have been studied or all doses can be given safely and can be given in conformity with the principle of the lowest effective dose being recommended.

So in this regard, our analyses suggest that there's actually little meaningful dose or concentration response across the entire range of doses that were studied. And, again, considering the phase 2 data, that goes from 10 milligrams to 80 milligrams, at least with regard to the objective measures of sleep latency and sleep maintenance, which again we think are probably more reliable and perhaps more useful than the subjective measures.

In particular, in the phase 3 trials, there's no clear exposure/response relationship, in

our view, for either objective measure -- that's latency of persistent sleep or WASO -- even at exposures that are seen with the 10-milligram dose, even though that dose wasn't studied in the phase 3 studies.

In that small phase 2 crossover study, the 10-milligram dose was clearly statistically significantly superior to placebo in the primary outcome of sleep efficiency, which isn't a particularly standard outcome but nonetheless is one that seems to provide useful information. It was statistically significantly superior to placebo on the WASO also, an objective measure of sleep maintenance.

The protocol-specified analysis was not significant at 10 milligrams in that study on LPS, the objective measure of sleep latency, but there were some carryover effects, which is a problem that can occur in crossover studies. So in at least one reasonable alternative analysis, which avoids that -- in other words, looking at first period data for the 10-milligram versus

placebo -- showed statistical significance on LPS as well.

So again, as I said, identifying the lowest effective dose is critical because of the next-day adverse events. And that is, in our view, an issue here as well.

Clearly, we think that next-day somnolence is dose-related, as is something that was termed excessive daytime sleepiness, which seems to be perhaps different from some just residual somnolence but is more acute, maybe sudden and involuntary in onset.

Most significantly -- and again, we'll hear a great deal about this today -- but most significantly, suvorexant at the doses studies in the phase 3 studies impaired driving in formal driving tests.

In the study of non-elderly patients, the driving study, a dose of 20 milligrams was impairing on the first day after the first dose the night before, and the 40-milligram dose was impairing on the first day after the first dose and

at the only other assessment a week later, as assessed by something called the symmetry analysis, which compares the patients who had marked deviation from the midline as compared to those who didn't. And you'll hear all about the specifics of the symmetry analysis, but it's an analysis that we have relied on in the past.

In the elderly driving study, the 30-milligram dose, while it didn't reach statistical significance, certainly approached statistical significance on both nights tested in terms of impaired driving. And the 15-milligram dose did not cause impairment, even numerically, in that study. But the 20-milligram dose did cause impairment, as I mentioned before, in the non-elderly study, and many patients who received 15 milligrams actually achieved plasma levels that overlap with those achieved by the patients receiving 20 milligrams. And that again is a dose that's been shown to be impairing.

So in our view, taken together, these studies suggest that suvorexant does or is likely

to cause driving impairment at doses as low as 15 milligrams the day after taking it.

These data are of particular concern on their own, but also because we know, as I said, that there was a dose-related increase in somnolence, which we know can be impairing. And we are also becoming aware or have become aware that patients who are somnolent or who have impaired driving aren't particularly reliable reporters of that phenomenon. They can't reliably tell that they are impaired or that they are sleepy.

There are other data, of course, that raise concerns about the safety of doses as low as 15 milligrams, including we know that women clear the drug more slowly than men. We know that obese people clear the drug more slowly than non-obese people. And these data taken together suggest that subsets of the population -- for example, obese women -- who may make up a significant portion of the population who would be candidates for treatment with suvorexant -- may have substantially elevated levels of suvorexant at doses as low as

15 milligrams with, of course, the attendant risks the next day. There are other adverse events, including a narcolepsy syndrome and, perhaps more worrisome, a dose-related increase in suicidal ideation.

So in summary then, the data taken as a whole suggest to us that the lowest dose studied, which is 10 milligrams, is an effective dose and that there's little to no dose- or concentration-response relationship over the studied dose range, at least on the objective measures of sleep latency and maintenance.

There is, though, a dose-response relationship for adverse events, including impaired driving the next day, which suggests, at least to us, that even the lowest doses studied in the phase 3 studies, 15 and 20, depending on the population, may be unsafe in some patients; and that the highest dose recommended, 30 or 40, may be unsafe for many patients.

Indeed, the lowest doses may be particularly unsafe in a subset of patients who I talked about,

in whom exposures at the lowest doses, 15 and 20, may be considerably higher than that.

So then these data, in our view, taken together argue for recommending doses as low as 10 milligrams, or even perhaps lower than 10 milligrams. Again, understand that if we think that there's really no dose-response or concentration-response relationship down to the dose of 10, it's possible that a lower dose and lower concentrations are equally as effective.

So as I say, these data, in our view, argue for recommending a dose as low as 10, although there is no 10-milligram dose available at the moment, and it's not proposed by the sponsor.

So these are the primary issues that we would like the committee to address. Of course, we're interested in any other relevant issues that the committee thinks is worth discussing.

Let me just say also that in our documents you can see that various reviewers of the data have taken positions on these issues, firm positions, and there isn't always agreement in the file among

FDA reviewers. That's not unusual. But I want to point out that we have not taken a final position on any of these issues. That's why we're here, and that's why we're asking for your input.

So at this point, I want to take the division director's prerogative to just make a personal statement. And I won't belabor this. But anyway, this is my last advisory committee meeting as an FDA employee.

So I just want to thank the committee, and certainly the invited members, for your service to the division, but of course, more importantly, to the public. And if any past advisory committee members are listening somewhere, I'd like to thank them, too, for all of their input and help and guidance over the years, over the 30 years that I've been here. It's been a privilege for me to have worked with you all and to have been part of the process over those years.

So I just want to thank the committee again from that perspective as well as for all the work that you have done in preparation for this meeting

and all the work that you will do today. So thanks very much, and with that, I'll hand it back to Dr. Rosenberg.

DR. ROSENBERG: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this

issue of financial relationships at the beginning of your presentations, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Sponsor Presentation - Nadine Margaretten

DR. MARGARETTEN: Good morning, ladies and gentlemen, members of the advisory committee, and FDA. I'm Dr. Nadine Margaretten from Merck Regulatory Affairs. Merck is very pleased to participate in this advisory committee meeting to discuss suvorexant, a first-in-class orexin receptor antagonist for treatment of insomnia.

The agenda for presentation is as follows. I will provide a brief introduction of suvorexant, also known as MK4305. Dr. Joe Herring from Merck's clinical neuroscience department will provide background on the medical need to treat insomnia and the scientific rationale for use of an orexin receptor antagonist for insomnia treatment. Dr. Herring will then present the clinical development program, with an emphasis on the phase

2 and 3 efficacy and safety results. Dr. David Michelson from Merck's clinical neuroscience department will then conclude with a benefit/risk assessment of suvorexant for the proposed indication of insomnia for adults.

In addition to the suvorexant project team, we have several consultants who have joined Merck today: Dr. Thomas Roth from the Sleep Disorders and Research Center at Henry Ford Hospital and Wayne State University School of Medicine;

Dr. Thomas Scammell from the department of neurology, Harvard Medical School, Beth Israel Deaconess Medical Center;

Dr. Eric Nestler from the department of neuroscience, Mount Sinai School of Medicine; and

Dr. Gary Koch from the biostatistics consulting lab at the University of North Carolina at Chapel Hill.

During the meeting, our consultants will be available to address questions regarding their areas of expertise.

So how does suvorexant work? Suvorexant is

a highly selective antagonist of orexin receptors 1 and 2, and it provides a novel mechanism of action for treating insomnia. By transiently blocking awake signaling, it allows sleep to occur.

Suvorexant helps patients by shortening the time it takes to get to sleep and by maintaining sleep during the night. The efficacy of suvorexant is evident with the first night of dosing, and it continues with chronic use. Our clinical program did not see any evidence of tolerance with continued use, nor evidence of withdrawal after stopping treatment. Furthermore, suvorexant is generally well-tolerated and with an acceptable residual effect profile.

Guidance from FDA has been incorporated into the program, including feedback from an end-of-phase-2 meeting as well as a pre-NDA meeting, and also from discussions with the controlled substance staff.

FDA input was incorporated into phase 1 trial designs and assessments, and also in the designs of the phase 3 trials. Based on the end-

of-phase-2 meeting discussion, we designed replicate studies to assess the efficacy of suvorexant that included both objective and subjective measures for both sleep onset and sleep maintenance, as required by FDA.

To support a chronic indication, efficacy assessments were conducted after 1 and 3 months of exposure in addition to after acute use. These combined endpoint trials evaluated two doses of suvorexant for each age population. Based on the content of our NDA, it was accepted for review last November.

The suvorexant clinical program consisted of 36 clinical trials with over 2800 patients and subjects treated with suvorexant, and of these, over 1700 patients were included in the phase 3 trials. The phase 3 program included replicate 3-month trials with objective and subjective endpoints and conducted in both elderly and non-elderly patients.

Also, a unique 12-month, placebo-controlled, long-term safety trial was also conducted in

patients with DSM-IV primary insomnia without insomnia severity inclusion criteria. This trial included monthly efficacy assessments and also a randomized discontinuation phase to assess relapse to insomnia.

Safety was also thoroughly investigated in our program, and this included prospective evaluation of adverse events associated with marketed sedative hypnotic drugs including, and importantly, residual effects.

We also assessed potential effects related to the novel mechanism of action and also CNS effects, including suicidality, withdrawal, rebound, and abuse potential. Special safety studies in populations were also evaluated in the program, and on-the-road car driving studies were conducted in both elderly and non-elderly subjects.

We believe that the data presented in our NDA that will be summarized for you today supports the efficacy and the safety of suvorexant for the indication of insomnia characterized by both difficulties with sleep onset and/or sleep

maintenance.

As summarized in the addendum to our briefing package, we have revised dose considerations. Specifically, the dose recommendation is to use the lowest effective dose for the patient. The usual starting dose should be 20 milligrams, or 15 in elderly. For patients whose insomnia symptoms persist and who have demonstrated acceptable tolerability to suvorexant, a dose increase to 40 milligrams, or 30 in elderly, may be considered.

At this time I would like to introduce Dr. Joe Herring, the clinical lead for the suvorexant program, who will present the clinical development program and the efficacy and the safety data on suvorexant.

Sponsor Presentation - Joseph Herring

DR. HERRING: Thank you, Dr. Margaretten.

Good morning, and on behalf of Merck and the suvorexant development team, it's my pleasure today to introduce you to suvorexant, a first-in-class orexin receptor antagonist developed for the

treatment of insomnia.

To orient you to today's discussion, this presentation will begin with a brief background on sleep and insomnia, including how sleep is measured. The rationale for orexin antagonism in the treatment of insomnia will then be explained. The remainder of my talk will focus on the efficacy and safety of suvorexant, concluding with Dr. Michelson's discussion of benefit/risk profile and dosing considerations.

In the next segment, I'll briefly tell you about sleep and insomnia, the diagnosis of insomnia, and how sleep is measured.

To begin by stating the obvious, everyone needs sleep, and we're all likely too familiar with the detrimental impact of sleep loss and sleep deprivation. Insomnia, or difficulty sleeping, is common, affecting up to a third of adults, and extracts significant societal costs due to accidents, healthcare utilization, lost productivity, and absenteeism. In the recent America Insomnia survey, analyzed costs due to

insomnia-related workforce reduced productivity were estimated to be $63 billion in the U.S. alone.

Insomnia is experienced by patients as a subjective disorder. That is, patients must actually perceive and report symptoms. A DSM-IV diagnosis of insomnia requires that patients report difficulty initiating sleep, difficulty maintaining sleep, or non-restorative sleep for at least a month.

Patients may experience one or more of these symptoms in combination, and over 90 percent of patients experience both difficulty initiating sleep and difficulty maintaining sleep at some point during their course. This difficulty sleeping must be accompanied by significant distress or perceived impaired functioning and not be due to another disorder.

While insomnia symptoms are experienced subjectively, insomnia can be measured both objectively by polysomnography in the sleep lab or subjectively by patient report in a sleep diary.

For the presentation of suvorexant efficacy

that's to follow, it's useful here to pause in order to highlight some key efficacy endpoints used in sleep research. These are also identified in the background package.

Using objective and subjective measurement approaches, PSG, or sleep diary, two major dimensions of sleep difficulties that people typically experience can be characterized, trouble with falling asleep or staying asleep. For example, reductions in the time it takes to fall asleep, or sleep onset, can be characterized objectively by the polysomnographic-based endpoint latency to persistent sleep, or LPS. In contrast, improvements in staying asleep, or sleep maintenance, can be evaluated through a sleep diary subjective report of total sleep time, or sTST.

Since insomnia is the patient's experience of their sleep difficulties, these subjective measures -- subjective total sleep time, subjective time to sleep onset, and subjective wake after sleep onset -- are particularly important in the evaluation of any new sleep medication.

Lastly, sleep efficiency is the percentage of time spent asleep during the time, or total sleep time, divided by the total time in bed, which is fixed in sleep lab at 8 hours, times 100. The sleep efficiency endpoint will be important in the discussion of phase 2b data, whereas the other five endpoints will be a focus of discussion of the phase 3 data.

In light of this brief backdrop on sleep and insomnia, we'll now focus on why an orexin receptor antagonist like suvorexant makes sense for improving sleep.

First, it's important to note that available treatments don't serve all patients equally well, and new treatments are needed for insomnia. The most commonly used treatments, benzodiazepines and the Z drugs, increase sleep through enhancing the activity of GABA, the brain's major inhibitory neurotransmitter.

While the shorter-acting benzodiazepines and the Z drugs may induce sleep well, most maintain sleep less effectively or not at all. Longer-

acting benzodiazepines like quazepam may provide maintenance, but with increased risk of next-day side effects. Few treatment options improve both sleep induction and have efficacy for sleep maintenance that's sustained throughout the entire night, with only limited next-day residual effects.

Suvorexant, a first-in-class orexin receptor antagonist, offers an entirely new approach to the treatment of insomnia. Genetic, pre-clinical, and clinical characterization of the orexin system has shown that orexin neuron activity promotes wakefulness, and that firing of these neurons decreases during sleep. Competitive antagonists of orexin neuropeptides at orexin receptors during the night selectively blocks the wake-promoting effect of orexins, thereby facilitating sleep.

Traditionally, GABA agonists have been used to treat insomnia, and now a different, more targeted approach, is possible through the mechanism of orexin provided by an orexin receptor antagonist. For instance, neurons producing GABA, the primary inhibitory neurotransmitter in the

brain, are widely distributed and represent about 40 percent of all neurons. In contrast, a limited pool of about 90,000 orexin A and B neuropeptide-producing neurons reside in the hypothalamus, a discrete brain structure, to connect with downstream wake-promoting centers.

Sleep therapeutics that work through GABA -- for example, zolpidem -- act by increasing the activity of GABA, which causes broad CNS suppression, whereas orexin receptor antagonists like suvorexant act by selectively attenuating orexin peptide wake signaling to achieve a unique clinical profile, as will be demonstrated in the data to be presented and discussed here today.

With that bit of background, I'd now like to tell you about suvorexant's clinical development program.

Suvorexant has been comprehensively studied in a program where exposure to suvorexant was extensive. 842 subjects and patients were exposed to suvorexant in 32 phase 1 studies, which included dedicated studies of respiratory safety, residual

effects, and abuse potential.

The efficacy and safety of suvorexant was examined in 254 insomnia patients in a phase 2b dose-ranging crossover study in which 243 patients received suvorexant at one of four dose levels. Three parallel group trials in over 2800 insomnia patients comprised the phase 3 program, in which 1,784 were exposed to suvorexant, including 160 patients treated for at least a year, which all told equates to about 758 person-years and more than 275,000 patient nights of exposure.

These trials, one long-term safety study and two pivotal efficacy studies, were conducted in a diverse population representing 24 countries and of whom 46 percent were elderly.

In terms of suvorexant's clinical pharmacology, some key takeaways from this summary slide are the suvorexant has a Tmax of about 2 hours and has a plasma half-life of about 12 hours. It can be dosed without regard to food, is metabolized via CYP3A4, and is unlikely to be a perpetuator of drug/drug interactions. We see only

modest effects on exposure with important intrinsic factor covariates, such as gender and BMI, of less than 25 percent.

To evaluate suvorexant efficacy and safety in the setting of insomnia, a phase 2b study in 254 DSM-IV criteria primary insomnia patients was conducted. This study was a double-blind, crossover PSG trial with 4-week treatment periods separated by a 1-week placebo washout. PSGs were performed in the sleep lab at baseline and after night and at the end of week 4 in each treatment period.

The trial comprised four 2-by-2 crossovers, with the ends as shown on the right panel, to evaluate four doses of suvorexant -- 10 milligrams, 20 milligrams, 40, and 80 milligrams. The co-primary endpoints in the study were sleep efficiency at night 1 and end of week 4, with key secondary endpoints of wake after sleep onset and latency to persistent sleep, also at night 1 and at the end of week 4.

We'll now be talking in more detail about

the phase 2 results, which are critical in understanding our phase 3 dose selection.

This slide shows the efficacy demonstrated in phase 2b for the primary endpoint of sleep efficiency. The graphic plots the difference from placebo in least mean squares and 95 percent confidence intervals for the improvements seen in sleep efficiency on the Y axis for the four doses of suvorexant, 10, 20, 40, and 80 milligrams, with the night 1 and end-of-week-4 time points on the X axis.

What we saw for the sleep efficiency endpoint was a dose trend at night 1, but not so clearly at week 4, and the 10-milligram dose was clearly the least efficacious at both time points.

In addition to sleep efficiency, key secondary objectives of sleep onset, LPS, and sleep maintenance, WASO, were also assessed in the phase 2b study. Here the Y axis shows the least squares mean differences from placebo in minutes and 95 percent confidence intervals for the two endpoints.

On the WASO plot on the right, you can see the dose response on night 1, where 10 milligrams is the least effective and 80 milligrams is maximally effective. As was mentioned, due to carryover effects seen only for the LPS endpoint in the study, we've displayed period one-only LPS results on the left panel, where in this analysis, unlike for WASO, there is no dose response for LPS.

Now, while these objective improvements we've just seen are substantial and encouraging, patients come to physicians with subjective complaints as insomnia, by definition, involves patient perception of sleep disturbance and clinically significant distress.

Assessment of improvement cannot be based solely on the laboratory measures. Patient-reported efficacy is critical. And based on our end-of-phase-2 interaction with the FDA, it was an expectation that we would demonstrate subjective efficacy at 3-month time points in two replicate trials in order to obtain approval.

In order to evaluate suvorexant's effect on

patient-perceived sleep, subjective sleep was also collected via daily e-diary. The analyses displayed here show subjective sleep improvements across three endpoints of subjective time to sleep onset, subjective total sleep time, and subject wake after sleep onset, averaged by week.

The Y axis shows the least squares mean difference from placebo in minutes and 95 percent confidence intervals, with the week 1 and week 4 results plotted on the X axis for each endpoint.

These results show that 40 and 80 milligrams consistently improved subjective sleep onset and maintenance endpoints, whereas 10 and 20 milligrams were ineffective for all subjective endpoints in the study.

Suvorexant was generally well-tolerated in the phase 2b study. This table shows adverse events occurring with an incidence of greater than or equal to 2 percent for the nervous system and psychiatric disorders categories.

While there's a lot on the slide, the main point to highlight here is that somnolence was the

most common adverse event, with a dose-related increase in somnolence seen up through 80 milligrams.

Having collected this tolerability and efficacy data, we were at a key data synthesis point for selection of phase 3 doses. Based on the totality of the profile, 40 milligrams was chosen as the primary dose, as it showed the maximum and most consistent efficacy.

Based on the mixed efficacy in the clinical data and agency feedback to test other doses in phase 3, 20 milligrams was chosen as a secondary dose. Doses flanking 20 and 40 milligrams were not selected. Ten milligrams had inconsistent efficacy broadly, and lower efficacy than 20 milligrams for sleep efficiency and WASO. And 80 milligrams offered no additional benefit over 40 milligrams.

Now, while the points just discussed provide the rationale for the non-elderly doses, we also planned to conduct combined age trials in phase 3. To achieve this aim, a dose adjustment for elderly was made to match exposures across age based on

phase 1 PK data in elderly that showed higher exposures in the elderly.

As displayed in the lower panel, this table summarizes the nomenclature used in phase 3 to describe the doses. An 30-milligram elderly dose was selected to match the non-elderly exposure of the 40-milligram non-elderly higher dose, or HD, and 15 milligrams in elderly to match the 20 milligrams non-elderly lower dose, or LD.

The upper panel shows the actual steady-state C-9hour data, or the exposure levels in patients 9 hours after dosing, from the subsequent phase 3 trials, illustrating that these age-adjusted doses achieved similar exposures across age groups.

Having established efficacy, safety, and doses from the phase 2b study, we set out in phase 3 with clinical program objectives designed to assess whether suvorexant improves both sleep induction and sleep maintenance; whether suvorexant is effective, both in the short and long term; and that suvorexant is generally safe and well-

tolerated, with special attention to evaluations of rebound, withdrawal, residual effects, and other potential mechanism-related questions.

Let's now focus on the phase 3 efficacy studies. First let's spend a minute looking at the design of the two pivotal studies.

These two similarly designed combined age and combined objective and subjective measure studies had three treatment arms, placebo control, and two active arms, suvorexant low dose and high dose. The core treatment period of these studies was three months, followed by a double-blind runout for assessment of rebound and withdrawal. One study, protocol 28, included an optional 3-month safety extension.

All patients in the studies provided subjective efficacy via the e-diary, and a subset of patients, about 75 percent of the sample, also underwent polysomnography at night 1, month 1, and at the end of month 3 and comprised a PQ cohort, who provided polysomnographic and questionnaire data.

This slide summarizes the statistical analysis methods used for these studies, with details provided in the meeting briefing package. Some items to note are that we evaluated the results across the typical covariates, had a multiplicity strategy to control type 1 error, and used the all patients treated data set for the analysis of safety.

In terms of the patient disposition in the two pivotal studies, we screened over 2800 patients in each trial to randomize the numbers shown across the treatment groups. Discontinuations due to adverse events were similar across treatments; for example, in protocol 29, the rates were 4.4, 4.2, and 4.8 percent for placebo, low dose, and high dose respectively. Likewise, the completion rates across treatments were high, on the order of more than 85 percent per treatment arm.

Regarding the demographics of the pooled data from the two trials, the gender split was as is typically seen in the insomnia indication, with approximately 64 to 65 percent of the patients

being female.

We also enrolled a substantial proportion of elderly in these combined age trials, with about 41 percent of the sample being greater than or equal to 65 years old. From a race perspective, white comprised the largest proportion, with fewer Asian, black, and other in the patient sample.

We can now focus our attention on the pivotal efficacy study results. These forest plots display suvorexant high dose onset efficacy. The least squares means and confidence intervals are plotted for each time point at night 1, week 1, month 1, and month 3 for the two trials, showing subjective time to sleep onset and latency to persistent sleep, with results on the side of the yellow arrow favoring suvorexant over placebo.

The take-home message here is that the results clearly indicate the statistically significant improvement associated with high dose treatment compared to placebo for both the subjective and objective sleep onset measures at both early and late time points in each trial,

with the exception of the month 3 LPS result in protocol 29.

Similarly, looking at the low dose results, you can see that the improvement associated with low dose compared to placebo was also generally evident across the endpoints and trials for low dose. However, the effects were numerically less than those observed with high dose.

Having reviewed suvorexant's effects on sleep onset, we now in the next few slides turn to suvorexant's improvements on sleep maintenance.

The setup for these forest plots is the same as for the onset plots, except now we're looking at subjective total sleep time, wake after sleep onset, and subjective wake after sleep onset maintenance endpoints, where again we have the time points on the Y axis and the least squares mean differences from placebo in minutes plotted on the Y axis for each panel.

As you can see, these results compellingly demonstrate suvorexant's effect in improving sleep maintenance across objective and subjective

measures, with replication of results across the trials and across the time points.

In looking at the low dose results, you can see that sleep maintenance improvement associated with low dose compared to placebo was also generally evident across the endpoints in the trials for low dose. However, in some cases the effects were numerically less than those observed with high dose.

This graphic displays another way of looking at suvorexant's maintenance effects throughout the night, as assessed by objective wake after sleep onset measured by PSG in the sleep lab. Adjusted mean change from baseline WASO in minutes with 95 percent confidence intervals are shown on the Y axis, and on the X axis, the pooled results for placebo, low dose, and high dose are shown for each third of the night.

Not surprisingly, the baseline means for WASO were lowest in the initial third of the night, only about 17 to 19 minutes, whereas the wakefulness was considerably higher during the

second and third thirds, 40 to 47 minutes and 55 to 60 minutes respectively.

The results shown here define a key attribute of suvorexant's efficacy profile, where both low dose and high dose improved sleep maintenance throughout the entire night, particularly in the last third, the span of time most affected in patients who have early morning awakenings.

Looking now at the differences from placebo and change from baseline across the two objective measures, LPS and WASO, this graphic shows that high dose consistently, for both endpoints and all three time points, provides greater improvement than the improvement seen in the suvorexant low dose.

High-dose suvorexant also consistently provides greater improvements in efficacy reported by patients than does low dose. Given that insomnia is a subjective disorder of patient-perceived difficulty sleeping, these substantial 1.5- to 1.8-fold increases achieved by high dose

over low dose across self-reported measures are an important aspect to consider in the overall assessment of the efficacy benefits possible with suvorexant.

Having completed our review of the core efficacy data, we'll now take a quick detour here to emphasize that in addition to the substantial magnitudes of effect demonstrated by standard sleep endpoints, patient perception of suvorexant's clinical benefits are also evident by other important subjective measures, in this case as assessed by the Insomnia Severity Index, or ISI.

The ISI is a 7-item scale of which the first three items pertain to sleep improvements and the remaining collect patient perception of their sleep satisfaction, problems with daily function, quality of life, and distress related to sleep. One accepted definition in the literature for a clinically meaningful response is a greater than or equal to a 6-point improvement in the ISI total score.

This slide shows the odds ratio for response

using the ISI responder definition of greater than or equal to 6 points improvement in the ISI total score using the pooled data for the assessment of suvorexant treatment versus placebo.

At both month 1 and month 3, the odds ratio for response both for suvorexant low dose and high dose was about twice that for placebo, indicating more patients on suvorexant achieve a clinically meaningful response as assessed by this measure.

The next few slides will summarize the third of the phase 3 trials in our program, the long-term safety study, or protocol 9. This was a randomized, double-blind, placebo-controlled, year-long, two-arm study where patients were assigned to either suvorexant high dose or placebo.

Following the 12-month core treatment period, patients entered a 2-month relapse assessment or a randomized discontinuation phase to look for return of insomnia symptoms. During the initial stage of this transition, rebound and withdrawal were assessed, and then relapse of insomnia was assessed in patients who switched from

suvorexant to placebo.

Regarding patient disposition in the long-term trial, over a thousand patients were screened to randomize 259 to placebo and 522 to suvorexant high dose. Discontinuation rates were similar between treatments, 37 percent on placebo and 38 percent on suvorexant, and consistent with expectations of a trial of this duration.

Discontinuations due to adverse event were slightly higher on suvorexant, 11.5 percent, versus placebo, 8.5 percent. Of those patients who stayed in the study for the entire year to enter the randomized discontinuation phase, the majority, more than 97 percent, completed the trial.

In terms of baseline characteristics, we saw a gender split in the study similar to what we saw in the pivotal efficacy studies, with about 55 to 58 percent being female. With regard to age, the majority, 59 percent or so, of the patients enrolled in the trial were elderly, with 18 percent on placebo and 14 percent on suvorexant being greater than or equal to age 75, so very elderly.

Most patients in the trial were of white race, with 8 to 9 percent being black or African American.

Patients reported their sleep efficacy via patient diary during the course of this 12-month-long placebo-controlled study, allowing for unique evaluation of long-term efficacy. The bottom right-hand panel shows the baseline means in minutes for the subjective efficacy measures, subjective time to sleep onset, subjective wake after sleep onset, and subjective total sleep time.

Interestingly, despite no set insomnia severity threshold requirements for entry to the study other than a DSM-IV diagnosis of insomnia, patients at baseline had difficulties similar to those in the pivotal studies, where they estimated about an hour to fall asleep by sTSO, an hour plus 10 or 20 minutes or so of awake time during the night, and a total sleep time of about 5 to 5 and a half hours.

Now, let's take a look at the plots of the data for these three endpoints, where change from baseline in minutes is plotted on the Y axis and

the monthly time points on the X. Looking at sTSO, for example, you can see reductions in sleep onset time provided by suvorexant, in closed yellow squares, over placebo, in open white circles, which is persistent and sustained over the entire year of treatment without evidence of tolerance to drug effect. This is also seen for the subjective wake after sleep onset reduction, shown in the top right panel, and in the bottom left panel showing increases in subjective total sleep time.

Of note, the nominal p values for these treatment comparisons were all less than .05 for all time points for all three endpoints, providing further evidence of suvorexant's utility in the long-term treatment of insomnia.

To summarize, what I've shown you in the data presented thus far is that suvorexant efficacy has been demonstrated objectively and subjectively for sleep onset and sleep maintenance in replicate 3-month pivotal trials. The efficacy was sustained over the course of a full year. Both the high and low suvorexant doses were efficacious and

consistent results were seen in elderly and non-elderly. High-dose suvorexant consistently delivered more efficacy across endpoints than low dose, particularly for the subjective measures. Sleep maintenance effects were seen throughout the night, and suvorexant's efficacy was perceived as meaningful to patients.

Having examined the efficacy of suvorexant in some detail, let's now turn our attention to the results of the safety analysis, an important aspect of any new sleep medication evaluation, beginning in the first couple of slides with a review of the methods used.

First, it's important to mention the time frames over which safety was evaluated in phase 3. As you'll recall, we had three phase 3 studies with different durations. By pooling data across the studies whenever possible, we gain the most precision in the estimates of safety. Since all three trials share at least a 3-month duration and because this corresponds to the primary efficacy evaluation of suvorexant, the zero to 3-month time

frame is our key safety database.

Additionally, the 12-month, long-term safety study and a 3-month optional extension in one of the two efficacy studies provide an opportunity to extend the safety examination of suvorexant high dose for zero to 12 months and of low dose for zero to 6 months. This extended duration data provides for further assessment of safety by overall exposure, and for assessment of less common adverse events, including serious adverse events and other events of clinical interest.

Given the special safety concerns associated with the use of sleep medications, we prospectively identified and assessed key events of clinical interest, grouped roughly into three categories, events potentially associated with the use of sleep medications generally, such as complex sleep-related behaviors, sleep paralysis, sleep-related hallucinations, excess daytime sleepiness, falls or adverse events associated with traffic or motor vehicle accidents; events pertinent to the evaluation of a novel CNS-active compound such as

suicidal ideation and abuse potential; and events of interest theoretically related to the novel orexin receptor antagonist mechanism of action, such as cataplexy.

A blinded external adjudication committee was put in place to evaluate potential adverse events of cataplexy and to evaluate falls in order to rule out that they were due to cataplexy.

This table displays the adverse event summary for the zero to 3-month pooled safety population. The percentage of patients who experience one or more adverse event is comparable across treatments, with modest dose-related increase in reported drug-related adverse events.

The incidence of serious adverse events was low and similar across treatments. Discontinuations due to an adverse event were 4.9 percent on placebo, 3 percent on low dose, and 6.2 percent on suvorexant high dose. Overall, both doses of suvorexant were well-tolerated.

Looking now at common adverse events that occurred at a frequency of greater than or equal to

2 percent and greater than placebo in the zero to 3-month time frame, you can see that somnolence was the most common and was seen with an incidence of 3 percent on placebo, 6.7 percent on low dose, and 10.7 percent on high dose. We'll be examining this adverse event of somnolence as it relates to suvorexant's overall residual effect profile in some more detail in the coming slides. Also included among adverse events that made this cut are fatigue and abnormal dreams.

Lastly, the safety profile seen here is similar to that seen with longer-term treatment with suvorexant low dose for up to 6 months and for suvorexant high dose for up to 12 months.

Before going further into the details of key safety data related to residual effects and events of clinical interest, I'd like to first mention a few highlights of the general safety seen in the suvorexant safety database.

Serious adverse events were uncommon and were observed at similar rates across treatment groups. No specific serious adverse events

occurred at a frequency of greater than .2 percent. Of four drug-related serious adverse events, one was on suvorexant high dose and three were on placebo.

Two deaths were reported in the program, one on suvorexant high dose due to hypoxic ischemic encephalopathy, falling or an accidental drowning, and one on placebo due to subarachnoid hemorrhage. Discontinuations due to adverse events were uncommon, with comparable frequency between the treatment groups. Somnolence was the most common reason for discontinuation on suvorexant high dose.

As mentioned, the longer-term safety profile seen over 12 months was similar to that of 3 months, with no new types of adverse events or an increase in adverse events to suggest an emerging safety concern. Lastly, no clinically meaningful differences were seen in safety across covariates of interest such as age and gender.

So in addition to the general safety we've just reviewed, a careful assessment of the potential for next-day effects is an important

aspect of fully characterizing a new sleep medication. Suvorexant's residual effects profile will now be summarized in the next segment of my talk, in which we'll look at several elements including adverse event reports, digit symbol substitution tests, on-the-road driving model, and phase 3 motor vehicle accidents and violations reporting.

As you can see in this grid, assessments of residual effects in the suvorexant program were extensive. Adverse events related to residual effects were examined across all phases of the development program, as were events of fall. The digit symbol substitution test, or DSST, an objective assessment of next-day psychomotor performance, was also assessed across the program phases.

In phase 1 studies, dedicated assessments of memory imbalance such as body sway and word learning tests, and other psychomotor performance tests such as choice reaction time, were also performed. Lastly, driving performance was

assessed in highway driving studies in phase 1 and through patient-reported motor vehicle accidents and moving violations in phase 3.

In the phase 3 program, next-day sleepiness or drowsiness reported by patients was captured as an adverse event of somnolence. A minority of patients experienced next-day somnolence in phase 3. As mentioned previously, this was the most common adverse event seen with suvorexant, occurring at a rate of 3 percent in placebo, 6.7 percent in low dose, and 10.7 percent in high dose in the zero to 3-month database. As will be mentioned in Dr. Michelson's talk later, these rates are comparable to those seen with other approved sleep medications.

Looking at the intensity of these events, most patients reported that the somnolence they experienced was mild to moderate, with only .2 percent and .6 percent of patients on suvorexant low dose and high dose, respectively, describing the somnolence as severe.

In the majority of cases, somnolence was

reported by patients in the first month of treatment, and discontinuation of therapy due to complaint of somnolence was rare, 0.2 percent on low dose and 1.7 percent on high dose.

In order to facilitate collection of more detailed information about cases of next-day sleepiness, some events of somnolence were termed excessive daytime sleepiness, or EDS, and were designated as events of clinical interest.

This designation of EDS did not denote the syndrome of EDS that is associated with other disorders. These were events of somnolence that were reported to be of a higher severity in terms of their duration or their intensity, and represent a subset of all the somnolence adverse events just discussed in my previous slide.

This table shows that EDS events reported in the zero to 3-month time frame occurred at rates of .2 percent, .6 percent, and 1.1 percent for placebo, suvorexant low dose, and suvorexant high dose respectively. EDS led to discontinuation in .8 percent of those in high dose versus .2 percent

of those taking either placebo or suvorexant low dose.

In addition to the assessments of patient-reported somnolence just described, we also assessed for potential next-day effects using the digit symbol substitution test, or DSST, a validated measure of psychomotor performance.

In the two pivotal phase 3 trials, the DSST was completed on the mornings following polysomnography at about 8 and a half to 9 hours after dosing on night 1, month 1, and month 3. By this assessment, both suvorexant high dose and low dose showed comparable results to placebo in the combined age mean data consistent with minimal next-day effects.

In order to further assess suvorexant's potential next-day residual effects, two similarly designed four-period placebo and active controlled on-the-road driving model tests were conducted. These test were done in an instrumented car with a driving instructor to ensure safety. One study each was performed in non-elderly, with an n of 28,

and elderly, with an n of 24, healthy subjects. Both the high and low doses of suvorexant were evaluated.

The test themselves, which consist of 1-hour-long highway drive, in which the subject is instructed to maintain position in the lane, were conducted on the morning after a single evening dose, on day 2, and after eight multiple nightly doses, on day 9. The positive control zopiclone at 7.5 milligrams was given as a single dose on the evening before the drive on day 2 and day 9.

The primary endpoint in these studies is SDLP, or standard deviation of lane position, which is essentially a measure of weaving. The primary hypothesis for the studies was that the true mean change in SDLP, the difference from placebo, would not exceed the standard threshold described in the literature, that is, that the hypothesis would be supported if the 90 percent confidence interval was below 2.4 centimeters. A secondary analysis of the data included a symmetry analysis of the change in SDLP.

Now I'd like to walk you through the results of these two studies, which are shown graphically on the right side of this slide. The non-elderly study is displayed above the elderly study, where for both studies the day 2 and day 9 mean SDLP difference's 90 percent confidence intervals are shown for the active control treatment, zopiclone, in blue, suvorexant high dose in yellow, and suvorexant low dose in orange. On the X axis, SDLP differences from placebo in centimeters increase toward the right.

The results show that the primary hypothesis for each study was met in that the mean SDLP changes and 90 percent confidence intervals for suvorexant high dose and low dose treatments were below the standard threshold of 2.4 centimeters.

Some patients elected to prematurely stop their driving tests in these studies. Four subjects in the non-elderly study stopped five drives out of 209, which is 2.4 percent. There were three drives on 40 milligrams and two drives on 20 milligrams. One subject stopped the drive on

placebo out of 103 placebo drives, for a rate of 1 percent.

All drives stopped by subjects taking suvorexant were requested by the subject, in contrast to the case seen with other hypnotics, where there's a 4 to 1 ratio the drive is being stopped by the investigator rather than the subject. Also, all stopped drives on suvorexant were associated with self-reported somnolence, indicating that subjects were aware that they were experiencing residual effects.

With that, we now turn our attention to the symmetry analysis of delta SDLP.

Symmetry analysis tests for an imbalance in the number of subjects with a change in SDLP above the prespecified threshold of 2.4 centimeters versus below the threshold at minus 2.4 centimeters. On the Y axis of this graphic is displayed the difference in SDLP on a drug-conditioned drive versus on a placebo drive in centimeters for non-elderly study on the left and the elderly study on the right.

In each case, the distribution of individual SDLP differences are shown for the day 2 and day 9 drives for both studies for both the lower, in orange, and higher, in yellow, doses of suvorexant and the active control, zopiclone, in blue. The change in SDLP differences for stopped drives are shown in magenta. By this symmetry assessment, a suvorexant treatment effect was observed on the driving task in the non-elderly study only, where an asterisk indicates significant asymmetry.

For perspective on this result, we will next examine the inter-subject variability possible between drives in this particular assay.

This slide again displays the individual subject delta SDLPs on suvorexant high dose and low dose conditions versus placebo for the non-elderly and elderly driving studies on the left panel, showing day 2 and day 9 results for suvorexant low dose and high dose, as in the previous slide.

However, to the right now is a new panel showing individual delta SDLP comparisons for subjects who performed two successive drives on

placebo. The inner left-hand panel shows comparisons between placebo drives and the two Merck studies for day 2 versus day 9, and on the farther right-hand panel is displayed placebo-versus-placebo drives for an external data set, reference below.

What this data shows is that there are individuals for whom drive-to-drive differences on placebo are similar to those seen in the suvorexant versus placebo comparisons in that delta SDLP values for a number of subjects also exceeds 2.4 centimeters.

An important conclusion from this data is that the symmetry analysis illustrates variability in this assay, as well as the arbitrary nature of the 2.4 centimeters threshold in reflecting actual impairment. Based on the observation of these placebo drive differences, individual SDLPs greater than 2.4 centimeters from drive to drive are not necessarily indicative of treatment-related impairment.

Acknowledging the observed treatment effect

on symmetry observed with this particular experimental task in the non-elderly study, it's also important to examine the potential risk of driving under real-world circumstances. To this end, we prospectively assessed report of motor vehicle accidents and violations in our phase 3 trials.

This slide summarizes the driving-related safety we prospectively assessed by patient-reported accidents and moving violations where the patient was the driver. This chart shows the results of the phase 3 assessment of potential suvorexant high dose effects in outpatient driving over the course of up to a year of treatment.

As you can see from the percentages of patients on suvorexant high dose versus placebo, for one or more MVAV events or for citations, the difference between treatment groups are comparable in that the 95 percent confidence intervals for the difference include zero.

Importantly, the rate of accidents reported by patients on placebo and on suvorexant high dose

are comparable, 1.4 percent on placebo versus 1.5 percent on suvorexant high dose, regardless of patient age or gender, in those who took suvorexant on an outpatient basis in real-world circumstances for up to a year.

However, while this data set doesn't provide evidence of an increased risk of accidents for patients taking suvorexant, it also doesn't rule out the possibility of risk. And as is the case with other sleep medications, patients and prescribers should be informed of the potential for next-day residual effects when taking suvorexant.

Now to summarize what we've seen in terms of suvorexant's next-day residual effects profile.

The assessment of the potential for next-day effects was comprehensive. The majority of patients, more than 90 percent, didn't report residual effects. Somnolence was the most common adverse event, but this effect was reported generally to be of mild to moderate severity and usually resolved with continued treatment. A minority of patients asked to discontinue

suvorexant high dose, 1.7 percent, due to somnolence, and this may be a treatment-limiting effect for some patients.

In terms of objective measures of next-day performance, including driving, most patients did not have evidence of meaningful impairment associated with suvorexant treatment. For instance, we saw no meaningful effects on the DSST in the combined age phase 3 assessment.

In the driving model, we saw no clinically meaningful effects based on the mean SDLP changes using the prespecified threshold. And as explained, the driving model symmetry results in the non-elderly study and the stopped drives do indicate a treatment effect in some subjects.

In a phase 3 assessment of driving in the outpatient setting, we saw an incidence of accidents and violations that was low and comparable across treatments. Lastly, similar results were seen across age with respect to the various assessments of residual effects.

In the last segment of my talk over the next

seven or so slides, the assessment of other important factors associated with the use of sleep medications will be discussed. Here we will cover several additional areas evaluated in the suvorexant program, including events of clinical interest, potential for mechanism-related effects, rebound and withdrawal, and abuse potential.

Earlier I described several safety categories and a rationale for tracking certain prespecified events of clinical interest. This table summarizes the phase 3 results.

As you can see, the occurrence of sleep-related adverse events of clinical interest were generally infrequent, with most occurring in the single digits and with a somewhat higher incidence on suvorexant high dose, acknowledging that some of these comparisons are difficult due to the low number of events.

In the assessment of terms potentially associated with the risk for abuse, the vast majority of instances were reports of simple drug administration errors, amounting to incorrect pill

counts. Lastly, the incidence of falls was similar across treatment groups, with no events adjudicated as cataplexy by a blinded external adjudication committee.

Given the association of aberrant orexin signaling with the condition of narcolepsy and because suvorexant is an orexin receptor antagonist, we'll pause here briefly to refresh your understanding of what narcolepsy is.

Narcolepsy is a chronic neurological disorder that's associated with degenerative loss of orexin neurons and results in the inability to regulate sleep/wake cycles normally.

The International Classification of Sleep Disorders diagnosis of narcolepsy includes excessive daytime sleepiness almost daily for at least three months, laboratory confirmation of short sleep onsets and REM sleep in a sleep latency test, and cataplexy is seen in some patients, which is an emotionally triggered episode of muscle weakness.

Based on our data, a small number of

patients, 1.8 percent, treated with high dose suvorexant reported either severe somnolence or EDS. All of these cases were reversible when the medication was stopped, and none were associated with other signs or symptoms suggestive of narcolepsy. For instance, no cataplexy was seen.

Regarding sleep architecture changes in patients who underwent polysomnography, especially with regard to REM-stage changes. There were no short REM onsets, meaning a REM latency of less than 15 minutes, in the five excessive daytime sleepiness cases for whom PSGs were available. There was one occurrence of a short onset REM in a single patient, who reported severe somnolence. But this was not replicated in this patient's other PSGs while taking suvorexant.

In summary, the profile we have observed in patients taking suvorexant nightly for extended periods of time, up to a year, are consistent with transient blockade of orexin receptors and not with a pharmacologically-induced narcolepsy-like syndrome. That said, suvorexant has not been

studied in narcolepsy patient and is therefore not recommended for use in patients with narcolepsy.

Another important area to consider with a novel central nervous system-active mechanism of action is the possibility of affecting suicidal ideation and behavior. Based on recent FDA guidance, we performed prospective evaluation of suicidal ideation and behavior using the CSSRS, or Columbia Suicide Severity Rating Scale, in phase 3.

As shown in this counts table, no cases of suicidal behavior occurred with any treatment. There was one report of suicidal ideation and intent but no plan in a patient taking suvorexant high dose.

In terms of suicidal ideation without intent, there was one case on placebo, one on low dose, and eight on high dose. Suicidal ideation was therefore infrequent, .1 percent on placebo, .2 percent on suvorexant low dose, and .7 percent on suvorexant high dose. All of these events occurred in the setting of factors associated with known risk; for example, in those with a prior history of

suicidal ideation or behaviors, concurrent depression, or other precipitating life events.

Notably, as assessed by an instrument called the Quick Inventory of Depressed Symptoms in the long-term safety study, suvorexant high dose had no effect on depressed symptoms in patients treated for up to a year. Nevertheless, the potential for suicidal ideation is a concern recognized in those taking sleep medications, and clinicians should be made aware that suicidal ideation can occur and that patients reporting suicidal ideation should be thoroughly evaluated.

Another important consideration in the characterization of a new sleep medication is assessment for the possibility of medication withdrawal or rebound insomnia symptoms.

In the double-blind runout phases of the phase 3 studies, we saw no evidence of symptoms of medication withdrawal, as assessed by the Tyrer Withdrawal Questionnaire or through reported adverse events of potential withdrawal in patients switched from suvorexant to placebo. Likewise,

rebound insomnia was assessed in the double-blind runout of the phase 3 studies by objective and subjective measures, as well as by patient report of symptoms suggestive of insomnia rebound. In these assessments, we saw no effects on measures of sleep onset. Effects seen on some sleep maintenance measures had characteristics of the return of insomnia symptoms, but did not appear to be consistent with clinically meaningful rebound.

Lastly, we examined the abuse potential of suvorexant. In nonclinical studies, suvorexant didn't have a profile suggestive of risk for dependence or abuse. In a formal abuse potential study in recreational poly-drug users with a history of sleep drug use, the reported degree of drug liking for suvorexant was similar to that of zolpidem, and both were different from placebo.

Abuse potential terms were also tracked across the program, and the incidence of these in phase 3 was low. As mentioned previously, the most common event was drug administration error or pill count discrepancies with no pattern consistent with

medication abuse.

Other events potentially related to abuse potential were rare, with a reported incidence of less than .4 percent in any treatment group, and there were no reports of euphoria in the phase 3 studies.

Having reviewed multiple dimensions of suvorexant safety, we conclude that the phase 3 program established a safety database in over 2800 subjects and insomnia patients with over 275,000 person-nights of suvorexant exposure. Suvorexant has an acceptable safety profile, with a low incidence of next-day residual effects. Few adverse events occurred at a frequency of greater than or equal to 2 percent and greater than placebo, with somnolence being the most common.

Across assessments, a dose-related increase in residual effects was observed. Abrupt cessation of suvorexant was not associated with clinically meaningful rebound insomnia or withdrawal. And lastly, suvorexant appears to have a low risk for abuse.

This completes the detailed review of suvorexant clinical efficacy and safety. Thank you for attention. Dr. Michelson will now discuss the benefit/risk of suvorexant.

Sponsor Presentation - David Michelson

DR. MICHELSON: Thanks, Dr. Herring.

My name is David Michelson. Good morning. I'm from Merck's clinical development group. And what I'd like to do now is to conclude our presentation by discussing with you the benefit/risk profile for suvorexant.

So as you've seen in the data that Dr. Herring has presented, suvorexant was studied in two pivotal 3-month studies as well as chronically in a one-year study. Suvorexant at the high dose of 40 and 30 milligrams and the low dose of 20 and 15 milligrams improved both sleep onset and sleep maintenance when they were assessed both objectively and subjectively.

That efficacy was maintained over a full year, and the efficacy was consistent for the non-elderly as well as for the elderly. And

importantly, as Dr. Herring showed you, suvorexant at the higher dose was maximally efficacious and consistently showed greater symptom reduction as compared with the 20 or 15-milligram low dose.

This dose-response is illustrated graphically in this slide, which you also saw earlier. So these are the subjective results. Each bar graph here shows the efficacy at the lower dose superimposed on that of the higher dose, and provides a visual representation of the relative efficacy for each dose.

What the data demonstrate is that for the subjective measures, the high dose consistently provided a mean response that's approximately 1 and a half to 1.8-fold, or 50 to 80 percent, greater increase in magnitude as compared with the lower dose.

Taken together, then, the totality of the results that Dr. Herring has presented in these data, the data strongly support the presence of a dose-response that favors the high dose for efficacy.

Dr. Herring has also reviewed the data that supports the safety and tolerability of suvorexant. During the clinical development program, the most common adverse event was somnolence that most often was mild or moderate and was dose-related. Next-day effects were limited in number and severity, and potentially mechanism-specific events of clinical interest occurred infrequently. Particularly importantly, there were no events that, after adjudication, were judged to be cataplexy.

So insomnia is an important medical problem. It's common. It's chronic. It affects the young. It affects the old. And it's associated with serious health concerns and social impact. And equally importantly, it's a source of significant distress and anxiety for patients. And unfortunately, the available treatments don't serve all patients well.

In particular, as Dr. Herring reviewed with you, the shorter-acting benzodiazepines and the so-called Z drugs induce sleep well, but most of

them maintain sleep less effectively or not at all. The older benzodiazepines induce and maintain sleep well, but it's often at the cost of increased risk, mostly in terms of next-day effects, falls, and suchlike.

There are few treatment options that are available to patients today that improve both sleep induction as well as sleep maintenance, and that sustain the improvements in sleep maintenance throughout the entire night while still retaining a favorable residual effects profile But the data from the clinical development program demonstrate that suvorexant does have the potential in its clinical profile to address that need.

Suvorexant improves both sleep onset and sleep maintenance, as you've seen. These are objective data. The subjective data, as Dr. Herring showed you, are similar. That effect on maintenance is sustained throughout the night and seen in the first third and the second third as well as the last third of the night. And these are effects that are seen on both the low and the high

dose.

Finally, suvorexant provides that efficacy without imposing an undue burden in terms of next-day effects. So as this slide shows, the frequency of next-day somnolence reported by patients taking suvorexant is comparable to shorter-acting drugs with less efficacy for maintenance.

What you see here is that the frequency of placebo-subtracted reports of somnolence for suvorexant corrected for time exposed to drug and juxtaposed with corresponding placebo-subtracted rates for the controlled-release form of zolpidem as well as for zopiclone, as reported in their product labeling. Despite having greater effects on sleep maintenance, suvorexant is not associated with large differences in next-day somnolence as compared with the other two drugs.

But efficacy ultimately is only important if patients perceive it as meaningful. And in fact, the data show that suvorexant's efficacy is perceived as meaningful by patients. As Dr. Herring showed you earlier in the clinical studies,

as measured by the Insomnia Severity Index and as compared with placebo, suvorexant was associated with an almost twofold increase in the odds ratio for achieving a response when response was defined using a generally accepted threshold.

Finally, as you've seen today, the safety and tolerability profile of suvorexant were maintained during chronic treatment. Over the course of a year and at the high dose, the clinical data do not suggest an association of suvorexant with unexpected risks, nor with late onset changes in safety or tolerability, nor with clinically meaningful rebound or withdrawal phenomena when treatment was stopped.

So to conclude, suvorexant is a first-in-class orexin receptor antagonist that specifically targets the regulation of wakefulness. Suvorexant is efficacious. It's efficacious for sleep onset. It's efficacious for sleep maintenance, and that efficacy is sustained throughout the night. It's efficacious for the elderly as well as for the non-elderly, and it's efficacious as early as night 1

and chronically over a year.

Suvorexant was generally safe and well-tolerated acutely as well as chronically. And suvorexant's clinical profile thus meaningfully expands the options that are available to patients suffering with insomnia.

What I'd like to do, then, is to finish by reviewing our proposed indication and our dosing recommendation. The indication that we're proposing for suvorexant is for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

With respect to dose, during the clinical development program both the high and the low dose were efficacious. Both were generally safe and well-tolerated for the non-elderly as well as for the elderly. And so in order to allow for individualized dosing, both doses should be available to patients and to physicians.

In terms of the specific dosing recommendations, physicians should use the lowest effective dose for the patient. The usual starting

dose should be 20 milligrams, or the 15-milligram dose for the elderly. And for patients whose symptoms persist and who demonstrate acceptable tolerability, a dose increase may be considered.

Thanks very much for your attention. That concludes our portion of the presentation.

Clarifying Questions

DR. ROSENBERG: Are there any clarifying questions for the sponsor? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. And in the interest of time, let me point out to the committee this is the time to ask questions to the sponsor; we'll be discussing amongst ourselves extensively in the afternoon.

Dr. Cohen?

DR. COHEN: Thank you. Jeffrey Cohen. So some clinical questions. I won't ask a whole series, though I have a lot. Optimal patient that you would recommend this medication to? I know that's probably premature.

Then I'm sure that some patients in the

studies had OSA. Not everyone had PSG. So what happened in patients that had obstructive sleep apnea with the medication?

DR. MICHELSON: Thank you. David Michelson from Merck. Let me respond to the optimal patient question as best I can, and then I'm going to pass it to Dr. Herring to speak to the OSA question.

In terms of optimal patients, we studied really a broad group of patients with insomnia. I don't think we have evidence to suggest that we can really pinpoint specific patient groups or specific individuals who are most likely to benefit or not benefit. So the short answer, I think, at this point is that it's probably premature for us to try and make a recommendation around that.

DR. HERRING: With respect to your other question about apnea patients in the phase 3 program, we did actually screen out patients in the PSG, for example. So we didn't have patients in the studies who had apnea. We did perform a dedicated safety study in apnea patients, however.

DR. COHEN: Do you want to just give me a

little bit of information about that? What happened with the OSA patients?

DR. HERRING: I'll ask Dr. Chan Beals to comment.

DR. BEALS: Hi. Chan Beals from clinical pharmacology at Merck. We did a dedicated safety study in about 25 subjects with mild and moderate obstructive sleep apnea. The primary endpoint was the apnea-hypopnea index and was measured on day 1 and day 4 in a crossover study where subjects were given placebo or 40 milligrams of suvorexant.

So on day 4 but not day 1, there was an increase in the apnea-hypopnea index of about 2 units, and there was no confirmation of that effect on day 1 when the full pharmacologic effects of suvorexant are present. And there was no difference in oxygen saturation.

DR. ROSENBERG: Dr. Rizzo?

DR. RIZZO: Thank you. I have a few questions. Probably most of them are for Dr. Herring.

I'm wondering what's the relationship

between the SDLP measure in the drive and real-world driving over extended time frames, or even a road test by an experienced professional. That's my first question.

DR. HERRING: I think actually I would ask Dr. Thomas Roth if he could comment on it.

DR. ROTH: I'm Thomas Roth. From the point of view of conflict, I serve as a consultant to Merck Pharmaceutical, and my laboratory, the Henry Ford Hospital Sleep Center, served as a scoring center for the phase 2 study. So those are my conflicts.

There are no studies which have attempted to look at the relation between SDLP as a measure and actual risk of accidents. So SDLP -- the closest thing that people have and why they tend to use 2.4 is because 2.4 is the level which is shown as an average of people on .05 BAC. But that does not mean that .05 BAC does in fact represent a risk.

So there is, to my knowledge, no data from any place, any source, which relates SDLP, whether in a simulator or on-the-road driving, to actual

risk of car accidents or frequency of car accidents.

DR. RIZZO: My next question is in the crash data that you presented, in the phase 3 trials, were the data controlled for exposure?

DR. HERRING: In the analyses submitted, there were crude estimates. But we do have those additional analyses, and they also show no difference.

DR. RIZZO: The crash data were self-reported. Did you validate the crash data against state records of crashes?

DR. HERRING: No, we did not.

DR. RIZZO: I have other questions, but probably there are other people who have some so I'll stop.

DR. ROSENBERG: Dr. Portis?

DR. PORTIS: I have a couple questions. One, in slide 70 you mentioned assessment by QIDS. So was that given to everyone, and how often? And also, were there any anxiety measures given to the patients in the study?

DR. MICHELSON: David Michelson again from Merck. The QIDS was administered in phase 3 at baseline to all patients, so in both pivotal studies and the long-term safety study. It was administered in the long-term safety study as well at multiple visits during the study, so if memory serves, at month 3, 6, 9, and 12, I believe, something like that. But it was not administered at the endpoint in the shorter of the 3-month studies.

So that's the QIDS. There was not a specific anxiety measure that was administered during the study.

DR. PORTIS: Were any other psychological assessments done at the beginning and throughout the 12 months?

DR. MICHELSON: That was the only formal mood assessment that was done, and there was not a formal assessment in terms of baseline, anything like the SCID or formal psychiatric diagnosis.

There was an informal -- not a psychiatric instrument, but an informal medical history that

included questions. But that was not a structured interview, and neither were there structured symptom measures that were performed through the study.

DR. PORTIS: And, I'm sorry, I have lots of questions, but one final one for now. You refer in slide 72 and 79 to comparisons with zolpidem. Do you have research on that that you did comparing the two head to head?

DR. MICHELSON: These are historical comparisons. These were not head-to-head comparisons.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: Bob Clancy. I have several questions for Dr. Herring. The first is that when the 209 patients took the driving test, five of them voluntarily stopped early because they were tired.

Then how do we interpret the real-world crash rates if in fact some of the patients felt unsafe to drive and voluntarily stopped driving, so only the alert patients were within that data set?

Do we know if patients stopped driving because they were somnolent and that's why the rates were comparable for the real-world accident rates?

DR. HERRING: There were not somnolence reports of -- is your question, did people that have accidents report somnolence?

DR. CLANCY: No. When you did the 1-hour driving test, five subjects withdrew early because they felt tired. How then do we interpret the real-world accident rates? Because some of the patients may have stopped driving because they felt too tired, and your data set only represents the drivers who were alert.

DR. HERRING: You're correct. We don't really have data on that issue.

DR. CLANCY: Okay. Second question is were there any subjects with a paradoxical reaction, where they actually had actually had worsening of their symptoms?

DR. HERRING: We did not formally look for paradoxical worsening. Not all patients respond equally to the medication.

DR. CLANCY: Okay. I just want to be clear. When were the subjects instructed to take the medication?

DR. HERRING: In the outpatient studies, just prior to going to bed.

DR. CLANCY: So a minute before they go to bed and so forth? Do we know from a PK point of view what their blood levels would be? If you're showing that there's a 10-minute reduction in latency to sleep, what levels are associated with that early 20-minute time period after they consume the medication?

DR. HERRING: We know the Tmax is 2 hours. There's an upslope that's occurring during that time. Maybe Rebecca Wrishko could comment on this.

DR. WRISHKO: Good morning. Rebecca Wrishko, clinical PK/PD. Perhaps we can bring up a slide depicting the concentration time profiles of both 20 milligrams and 40 milligrams after single-dose absorption, so slide 1322. Slide up, please. Thank you.

In this particular depiction, what we have

is 20 milligrams and 40 milligrams administered as a single dose to non-elderly subjects. And what we do see is a rising concentration time profile quite early after following oral administration of this particular entity.

Typically, as Dr. Herring pointed out, Tmax occurs within 2 hours, and the range is .5 hours to 6 hours.

DR. CLANCY: Okay. And then the last question for Dr. Herring is, I have to assume that once patients with insomnia find a medication that they like, that helps them, that they continue on these meds indefinitely. There must be data that says once a patient starts treatment, they don't stop after 3 months or 6 months.

Do we know what percentage of patients continue for years? Because I've only seen -- your data only covers 160 patients for 12 or more months. Do we know how many patients stop after 3 months; they're fine? Five years?

DR. HERRING: In terms of patterns of hypnotic use? Maybe I could ask Dr. Roth to

comment on patterns of hypnotic use in chronic insomnia.

DR. ROTH: There are several population-based studies on the use of hypnotics, and it's a bimodal distribution. Actually very few people use them 3 to 6 months. The population is bimodal.

There are people who tend to use it more than 30 times a year, something like that; and about 10 percent of the population, of the insomnia population, who use hypnotics use them nightly for well over a year. So it's about 10 percent of hypnotic users who will use at that.

It's very important to understand, though, that this is the first double-blind, placebo-controlled, one-year study. The previous longer study was an outpatient study by Andy Krystal and myself on 6 months of zopiclone. So this is double the longest study using both objective and subjective assays.

If I could go back for one second, if I'm allowed to ask you a question about the stop driving. I think your point is actually a very,

very good point. And that is that in this study, the five people who stopped driving all said I don't feel alert. I need to stop driving.

In contrast, in the literature, which I think will be presented later on, in the studies of previous hypnotics, 80 percent of the stopped driving were done by the instructor, not by the patient.

So you're right. People on this medication seemed to know when they're impaired. So you're right. Many people who might have not been able to drive in the one-year study may not have driven because they were somnolent. And you're right. We don't know if you force those people to drive, what would be the accident rate in those people. But I think it's important to understand that people do voluntarily not drive. And in fact, as we said, all five stops were, in contrast to previous drugs, decided by the subject.

DR. CLANCY: Thank you.

DR. ROSENBERG: My turn. I have three questions. I'll just ask them, and you guys can

decide who's going to answer.

First is, do you have any data on the effect on sleep architecture? Do you have any data on other cognitive measures, particularly short-term recall, short-term episodic recall? Do you have any data on the efficacy or adverse events in patients with preexisting cognitive impairment, such as dementia or mild cognitive impairment?

DR. HERRING: Thank you for your questions.

In terms of the sleep architecture changes seen with suvorexant, we had the opportunity to look at that in detail in the phase 3 studies where we had the polysomnographies performed. We had PSGs on night 1, month 1, and month 3.

Overall, looking at the architecture changes, we see that there are proportional changes in the different stages of sleep relative to the increases in total sleep time that we see for all stages, for the most part, except for REM stage, which has a small increase of less than 4 percent at night 1, and then that decreases in the subsequent polysomnographies.

Maybe you could go to your third question about whether we studied in mild cognitive impairment or patients with dementia, for example. And we at this point have not performed those studies.

To the second question, we'd actually ask Dr. Chan Beals again to comment.

DR. BEALS: Chan Beals, clinical pharmacology. Can I clarify your question, though? You're asking about short-term effects, or are you asking about did we have other measures the next day?

DR. ROSENBERG: No. I'm asking about other cognitive measures, specifically short-term recall.

DR. BEALS: Yes. Well, short-term recall was used. Immediate and delayed word recall was used in a middle-of-the-night waking study, and the results there, suvorexant had no effects and neither did the positive control, zolpidem.

That test was also used in, I think, four clinical studies the next morning. And in three of the four studies, there were no effect. There was

one study, which was the non-elderly driving study, that there was a statistically significant effect of word recall for suvorexant on the high dose on, I think, day 2. That amounted to two words. That's of questionable clinical meaningfulness.

DR. ROSENBERG: Thank you.

Dr. Schwartz?

DR. SCHWARTZ: Thank you.

As you said, insomnia, the most important outcome is whether patients feel better. So the Insomnia Severity Index is really important. So I just want to -- first as a point of clarification, that the percent with a clinically important difference in the low dose versus the high dose at 3 months was identical, right? It was 56 percent versus 55 percent, and pretty similar in the low dose versus high dose. Right? Thirty-four percent and 40 percent at 1 month. Is that right?

DR. HERRING: Yes. Those are the responses.

DR. SCHWARTZ: Okay. So then my second question is why did you decide -- I mean, my question is why did you decide to set the threshold

at 6 points? In the literature, I've seen a variety of definitions of the clinically important difference, why you chose that one. And more importantly, could you provide us a full distribution of the change scores on ISI so we can see with different categories, in the low dose and the high dose and the placebo group, how many people changed by different amounts.

DR. HERRING: Maybe I could ask Dr. Roth to comment on the 6-point threshold score.

DR. ROTH: The person who developed ISI is Charles Morin. And in the Journal of Sleep in this past year, he validated 6 points. He validated 6 points in a paper in Sleep this year as going from clinical insomnia to non-clinically relevant insomnia. So that's from a paper by Morin.

DR. SCHWARTZ: Actually, I found a Morin paper in Sleep from 2011 where he sets it at 8.4 and talks about 9 as a threshold for a very important benefit, and 8.4 as a clinically important effect. So that's why I was just wondering about that.

DR. ROTH: Yes.

DR. SCHWARTZ: So the same person?

DR. ROTH: Right.

DR. ROSENBERG: Dr. Chervin?

DR. HERRING: I'm sorry. Maybe in terms of your other part of the question about distributions, we did not submit those types of analyses in the filing. But those are possible to be done, and we do have some data around that.

DR. CHERVIN: I had a question about the two large phase 3 trials. They both produced quite impressive numbers of patients and p values, but there were some differences in the outcomes, for example with LPS.

But there was also, I think, if I remember in reviewing the materials, a difference in the impression of the dose-response relationship between the two trials. And I was wondering if anyone from Merck had any comments about what would have accounted for different results in those two very similar large trials.

DR. HERRING: You're asking about the LPS

result in the one study at month 3 time point?

DR. CHERVIN: LPS, and also in your view whether -- I seem to remember that the dose-response issue seemed different in the two studies.

DR. HERRING: Well, in terms of the LPS result in the one study, we did see effects that were evident on night 1 of about a 35-minute reduction in LPS from baseline. And that effect was actually sustained, more or less, at about a half-hour reduction from an hour of onset time through the 3-month time point. But we also saw increasing placebo response in that one trial, which most likely explains the difference between the results in the two studies.

I was less clear about your question about dose-response. Dr. Michelson?

DR. MICHELSON: Thanks. David Michelson from Merck. I want to actually follow up on Dr. Herring's response first. Could you put slide 34 up, please? Yes, please. Slide up.

These are forest plots that look at the high dose. I guess I would argue -- so they're not

exactly the same, although there are confidence intervals that are clearly overlapping here.

I think in any clinical trial, again, there's a certain amount of variability. The trials were not done in the same place. One of them included large numbers of Japanese patients, which had to do with both using different areas but also regulatory requirements for Japan.

They're different studies. You don't expect the same results. I think, though, that the pattern of the results is pretty similar for both studies, and certainly consistent. And slide 35, please.

Again, similarly, I think for the low dose, you see the same sort of pattern. At month 3 you also do get -- you're getting further away from baseline values. You're getting some drift in the population so that there's also more noise, I think, that comes in, and you do see a little bit more variability. But I don't think these suggest that there are really marked differences between the trials.

Can you repeat the question on dose-response, please?

DR. CHERVIN: I think one of the issues that's going to come up later is both for the effectiveness and safety issues. Is there a dose-response difference? And I was asking whether, in your impression, the two trials suggested anything different between -- a different effect or safety issue between high dose and low dose.

DR. ROTH: No. I think they're both consistent in terms of their response. I think what you see consistently is that the high dose always looks better. It's not a statistical comparison, but it always - numerically -- so if you were to do a non-parametric, you would always find the high dose with the numerically better response consistently on all endpoints at all time points. And those are consistent.

On any individual measures, the dose-response may be less pronounced or more pronounced. The ISI we just talked about, for example, it's less pronounced, particularly at the 3-month

endpoint. But there is a dose-response that's consistent.

For the objective measures, it's shallower. It's about 1.1-, 1.2-fold, so 10, 20 percent higher at the high dose; for the subjective measurement section, much more pronounced in the pooled -- when you take the pooled data, it's something on the order of 50 to 80 percent greater across all the subjective measures.

DR. CHERVIN: Thank you.

DR. ROSENBERG: Dr. Zivin?

DR. ZIVIN: Can I ask both the sponsor and the FDA to respond to my questions at this time? Just the sponsor? Okay.

Benzodiazepines have been used for many years, quite successfully. Why is suvorexant better than that?

DR. MICHELSON: David Michelson from Merck. I don't think we'd want to argue that suvorexant is better than them, and we've not compared them directly. I think what we would argue is that it's different from them. It's different in terms of

mechanism. In terms of the clinical profile, what we've showed you is that it has onset maintenance, maintenance through the night without -- or at least appears not to have some of the liabilities of the longer-acting benzodiazepines. But I think in terms of comparisons, it's hard for us to go far beyond that since we really don't have direct comparisons.

DR. ZIVIN: Okay. How serious has the suicidal ideation problem been with this drug as opposed to others?

DR. MICHELSON: Right. Suicidal ideation was reported in one patient on placebo. Where was one patient on the low dose, and there were, I believe, nine patients on the high dose, or .7 percent. So two comments around that; first is looking at the individual cases, all of them have confounding -- confounding is perhaps not a good word -- they have factors that would account for the suicidality in terms of history, in terms of stressors at the time of the event.

They were generally transient and fleeting.

One of them had suicidal ideation during the run-in as well as during the event -- as well as on drug, another in the context of stopping an antidepressant.

As compared with the epidemiologic data, both in the general population as well as in data that's been gathered with the CSSRS, the risk for suicidal ideation didn't look like it was higher. So the risk for suvorexant may in fact not be elevated.

Nonetheless, there is an imbalance. And suicidality is an important potential safety issue in the insomnia population, particularly given the risk for comorbid psychiatric disorders.

So what we would say is that as with other hypnotics, we believe this can and should be appropriately handled in labeling, and we have proposed label language similar to that that's used for the other hypnotics.

DR. ZIVIN: Okay. Now that you've heard what the FDA has to say, what do you think the dose is that you're going to recommend for elderly

people?

DR. MICHELSON: We're happy to talk further about that. I think at this point our position is we studied the drug with 40/30 for non-elderly/elderly and with 20/15 for non-elderly/elderly at the lower dose. We think that the incremental or residual effects, particularly at the 15- and 20-milligram dose, are pretty limited, certainly even as compared with placebo, and particularly put against the benefit of the efficacy that's received. At the higher dose, we would not recommend going to the higher dose unless you don't have efficacy at the lower dose and you've tolerated the lower dose well.

In terms of do you need different doses for the elderly and the non-elderly, I think that's certainly -- it's a perfectly reasonable question. We'd be happy to discuss it and to work with the agency around that.

DR. ZIVIN: Okay. What are the effects of accidental or deliberate overdose?

DR. MICHELSON: We really have relatively

limited experience with large overdoses. The experience we do have is from clinical pharmacology. I can ask Dr. Beals to speak to that.

DR. BEALS: Chan Beals from clinical pharmacology again. We did deliberately study doses up to 240 milligrams in single doses, and the effects are similar to those that were reported in the phase 3. So the top adverse events include somnolence and some dizziness, some fatigue, dry mouth.

Did that answer your question?

DR. ZIVIN: So you didn't have anybody who overdosed so badly that something bad happened to them?

DR. BEALS: I see. Okay. Overdose specifically. Yes. There was an accidental overdose case that occurred in a phase 1 unit, where an individual with COPD in a COPD stage 3 study was misdosed by the staff with 260 milligrams of suvorexant instead of the intended 40 milligrams. That individual reported no adverse

events. His oxygen saturation stayed above 90 percent throughout the night. His baseline O2 sat was 95 percent.

DR. ZIVIN: Okay. Do you have any fundamental disagreements with the FDA about their interpretations of your data?

DR. BEALS: Well, I think that's really a benefit/risk question, and I'd ask Dr. Michelson to speak to that.

DR. MICHELSON: Thanks. David Michelson from Merck. I think there were a lot of points made. I don't think it's probably useful to go through point by point. I think there are a number of things we agree with in their assessment. There are things that we are perhaps not in agreement with.

If you're asking about the major question, which I think the FDA has raised, it's really around the 10-milligram dose, our feeling is we did not see evidence in the phase 2 study that felt compelling enough to bring it into phase 3, and we really haven't studied it beyond that.

I don't think -- I can ask Dr. Wrishko or Dr. Stone to speak to this -- that we agree with the exposure analysis the FDA has done around the likely -- essentially, the predictive value of the exposure for efficacy.

DR. ROSENBERG: Dr. Zivin, I'll have to interrupt you and get back to you because we've got a lot of people waiting. We'll come back if we have time at the end.

DR. ZIVIN: Okay.

DR. ROSENBERG: Dr. Rosa?

DR. ROSA: Thanks. I'll try to be short. One design question, one sleep question, two waking questions. My somewhat naive design question. Sleep efficacy is compared to a placebo control group, but the waking outcomes are compared to active controls. I'm just curious about the rationale behind that. I'll start with that one.

DR. HERRING: Thank you. Certainly, to show the effectiveness of a sleep medication, it's an expectation in trial design, you would have a placebo arm for comparison of effectiveness.

Then I think the simple answer, the short answer, for the question of residual effects is that it's assumed placebo will have low residual effects. And the interest is to be able to benchmark that against other compounds that may have evidence that's known of residual effects. So, for example, in the driving study, we used zopiclone 7.5 milligrams because that's the standard and known to cause SDLP changes in that assay.

DR. ROSA: So that just raises this curiosity about efficacy against other drugs that are on the market, but I'll leave that for further discussion.

On the sleep side, any remarkable differences in stage 1 sleep, to get back to the sleep architecture question?

DR. HERRING: No. We did not see changes in stage 1.

DR. ROSA: Two waking questions. If I remember my reading correctly, the waking tests were done -- for example, the driving test -- in

the morning shortly after awakening, maybe at hour 9 after drug administration. I'm curious about other circadian-sensitive times of day, for example, midafternoon sleepiness, whether there was any consideration of testing drug effects at that time.

DR. HERRING: We did no formal testing of residual sleepiness after the time that was assessed in the car-driving studies.

DR. ROSA: Okay. Then in our studies of sleepiness among workers, oftentimes we get a very sensitive response to reaction time, which is not confounded by learning effects, which some of these other tests would have.

So I didn't see very much talk about reaction time effects in any of these studies. I'm just curious, what's the big difference here since somnolence or sleepiness seems to be an issue as it is with our shift worker tests?

DR. HERRING: Thank you for your question. I think Dr. Beals will have the information regarding that.

DR. BEALS: In the clinical pharmacology program, we used a number of instruments to look at reaction time, like the simple reaction time that was used in the single ascending dose study. And at doses above 50 milligrams, we do see a decrease in reaction time.

In the middle-of-the-night dosing study in the elderly, there was a choice reaction time that was measured. And there were effects at 1.5 hours for suvorexant, different than placebo. Those effects are gone by 4 hours. I think that those are the kinds of data that you're looking for.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: I want to go back to the question of suicide and depression. As you know, depressed patients have insomnia, and a psychiatrist will always give some hypnotics to depressed patients.

Did you try to pull out from your studies patients who had a history of a major depressive disorder or depression and try to see what were their response to your drug? Or do you plan to do

that? That would be my first question.

DR. MICHELSON: Thank you. This is David Michelson again from Merck. In terms of evaluation, as I said, patients had QIDS at baseline. So what we had was not a formal diagnostically ascertained entity of depression, but we did have a systematic measure of level of depressive presence or absence and severity of depressive symptoms at baseline.

In the two pivotal studies, we did not allow patients who had anything more than mild symptoms, so a QIDS of about 10, or patients who had a formal diagnosis of depression. However, in the long-term safety study, patients were allowed in with a QIDS up to 20, which really corresponds to pretty significant depressive symptoms, where a cut point typically is around 10.

In that study, we looked at a QIDS baseline endpoint. We looked at QIDS categorical; so to look where there are outlier changes in terms of, are there small numbers of patients going different ways in either group? The short answer was there

was nothing to suggest an effect on mood and particularly an effect on depression in those studies.

We then looked at the -- it essentially splits. So we looked at patients who had QIDS scores less than 10 at baseline, so essentially asymptomatic or only mildly symptomatic, and patients who had scores above 10 who were more prominently symptomatic. And, again, there was no suggestion that there was a differential effect in each other of those groups or that suvorexant was driving an effect on depression.

I can show you, if you can give me slide -- why don't you give me 959, please. Yes. Slide up, please. So this shows you at change from baseline, which is in the next to the last column, for the placebo and suvorexant groups from month 1, 3, 6, 9, and 12. So as I said in response to an earlier question, we measured at 3-monthly intervals.

What you can see is that throughout the study for the entire group -- this is now whether

below or above 10 at baseline -- there was no change in mean QIDS, and no difference amongst the placebo and treated groups. Next slide, which is 960, I believe.

Now you're looking at those patients who came in with scores greater than or equal to 10. So these are patients who had some significant measure of depressive symptomatology at baseline. And, again, there's no real suggestion of a treatment difference nor of an effect, really, in either group as you look over. The numbers are a little more variable, but the numbers, of course, are also smaller here.

Slide 961, please. Yes. Slide up. These are the patients who had baseline scores less than 10. So these are the patients who had, at most, mild symptoms or no symptoms. Again, really no change in mean scores over the course of the study for either the placebo or the suvorexant group. And then if you could finally put up for me slide 962. Yes. Slide up, please.

So this is essentially a shift analysis,

where we take those patients who, wherever they started, had either no change, an improvement of one category, an improvement of two categories, or, conversely, who worsened by one category, by two categories, or three categories.

Here you see placebo and the suvorexant high dose, and the numbers and proportions of patients in each group who changed in each category. And what you can see again is that there's no suggestion of a real difference between treatment groups in terms of a categorical worsening, suggesting that we're not able to identify any particular group of patients who are at particular risk.

DR. GUILLEMINAULT: My second question concerned shift workers. I don't know if you looked at shift workers, but you are going to take the drug during the daytime compared to your usual insomniac that are going to take the drug in the evening.

DR. MICHELSON: Right.

DR. GUILLEMINAULT: Did you see any

difference in the efficacy if you had any --

DR. MICHELSON: Yes. We did not do a study in shift workers. We don't have data in that population.

DR. ROSENBERG: In the interests of fairness and time, I'd like to ask people to restrict their questions to one. It's a very productive session, but pretty long.

Dr. Hoffman?

DR. HOFFMAN: I was wondering what the initial recommended dose would be in an obese, elderly female patient. And secondly, will the tablets be scored to allow for more individualized dosing? Thank you.

DR. MICHELSON: David Michelson again from Merck. Let me answer the last question first. The answer is the tablets are not scored.

DR. HOFFMAN: They're not scored?

DR. MICHELSON: They're not scored.

DR. HOFFMAN: Are they still uncoated or --

DR. MICHELSON: It's a heat-extruded tablet. I don't know if someone -- if you have more

questions on that, I'm going to defer them to someone who knows more about formulation than I.

DR. HOFFMAN: I was just thinking that if you have a patient that might --

DR. MICHELSON: They're not easily scorable.

Since the FDA did bring up the issue of risk related to obesity and gender and suggested that while both of them alone might have a modest effect, perhaps if you put them together you would have a large effect in terms of risk for, presumably, next-day effects. We did look at that, and we can also tell you a little bit about the exposures.

I think what would be most useful, though, would be to start by looking at the clinical data in which we basically looked at obese and non-obese women. And we looked at next-day somnolence and asked, okay, so is there actually evidence that there is some risk for increased next-day events? And somnolence being the most frequent, presumably it would be the most sensitive.

Could I have slide 2066, please? Thank you.

For the overall population, the most common next-day effect, as I said, is somnolence. And to assess whether risk is increased in that group, we looked at frequency of reports in patients who are obese, meaning a BMI greater than 30, and non-obese, BMI less than 30.

What you can see in the table is that the difference in reports of somnolence between the groups -- and these are small; for the high dose it was 10.2 and 8.3, placebo subtracted; for the low dose, it was minus 1.9 for the low and 7.5 in the non-obese women. So it actually goes in one direction in one group and in the other direction in the other group.

Basically, this does not suggest that there's really much evidence for difference between the groups. At least clinically, we're not seeing evidence that suggests a major difference in risk in these groups.

Obviously, given the finite number of patients who have obesity, the precision around the estimates is finite. And we can't rule out the

possibility that there's some difference, but certainly there's nothing in the data that suggests a large magnitude of a difference.

We also did a sort of sensitivity analysis for this, in which we went and looked -- we did a regression analysis. We looked at reports of somnolence in terms of relationship to body mass index. There was none. There was no interaction there. So that analysis essentially gave us the same result.

Could I ask Rebecca, could you come up and speak to the exposure issue that underlay the concern?

DR. WRISHKO: Rebecca Wrishko, clinical PK/PD. With respect to the overall exposure analysis, that was cited by the agency in the background document as well as in some of their other materials, we differ in the interpretation of the magnitude of effects in comparing the pharmacokinetics of suvorexant across body mass index. Slide up, please.

We conclude that obese females would have a

less than 20 percent increase in suvorexant exposure compared to those with normal body mass index.

Specifically, we conducted two analyses, one based on data from 321 healthy subjects from phase 1 studies identified in the phase 1 model-predicted column on the slide that is now in front of you, and another based upon the concentrations collected in the morning after bedtime administration of suvorexant from approximately 1640 patients in the phase 2/3 trials. And that was defined as a C-9hour analysis based on the tabulation.

Generally, the results of the two analyses, based on both the AUC and C-9hour, are consistent when comparing the groups to the central tendency of body mass index across these phases of study. And in this case, across both, median body mass index was approximately 25 kilogram per meter squared in both analyses such that then the comparison was made to the central tendency of normal body mass index, with a magnitude of the effect being slightly higher in the phase 1 model.

The agency emphasized the phase 1 analysis.

Slide 1312, please. Slide up. So here we have frequency distributions with respect to the phase 1 and the phase 2/3 data that were analyzed. And it's important to highlight the limitation of the phase 1 model in predicting concentrations based upon the extreme body mass values.

Here we really need to compare the left panel, the phase 1, to the right panel, the phase 2/3. So not only are the counts higher in the phase 2/3 analysis, so reflecting absolute count of subjects, the broad range of body mass index represented from phase 2/3 extends beyond that represented in phase 1 and provides important information that leads to our conclusion, that body mass index has a small impact on suvorexant exposure.

With respect to phase 1, predictions based on the extremes of these values, so where there's limited data beyond 32 kilogram per meter squared or perhaps less than 20 kilogram per meter squared, leads to low imprecision of AUC predictions.

Slide 1313, please. Slide up. So from the phase 2/3 analysis, from the observed C-9hour data again collected from individuals after bedtime administration across approximately 1640 patients in all, looking specifically at 40-milligram administration, what we find are modest differences only, modest differences between obese and normal which are less than 20 percent, and similar to any differences between overweight and normal individuals. And this is consistent across female and male subjects. We believe that this is a small difference, less than 20 percent, and does not require a specific dose adjustment based on body mass index or gender.

DR. ROSENBERG: Dr. Johnson has just advised us of formulation-specific questions.

Okay. Never mind. Dr. Mielke?

DR. MIELKE: Were there any interactive effects with the drug with psychotropic medications in terms of either adverse effects or efficacy, particularly with anti-anxiety drugs?

DR. BEALS: This is Chan Beals again from

clinical pharmacology. We did an alcohol interaction study as a representative of a depressant drug, and this was dosed during the day. Healthy individuals were given 40 milligrams of suvorexant or alcohol to deliver a blood alcohol concentration of .08 percent, the combination, or placebo.

The primary endpoint there was the digit vigilance test, and that was chosen because alcohol is quite sensitive to the effects, which were seen under the alcohol condition at 1 and 2 hours.

Suvorexant didn't have any effect in that study at any time point, but in combination there are additive but not synergistic effects at hour 2 and hour 5. But by hour 9, which was the last observation, everything had returned to the baseline placebo level. So that was the drug interaction study that we did with a depressant.

You asked about anxiolytics. There were no drug interaction studies done with that class. We did do a drug interaction study with paroxetine as a representative of a sedating antihistamine -- or,

sorry, antidepressant -- and there was no PK or PD interaction. In that study done, again, in healthy individuals, suvorexant was dosed at 40 milligrams and paroxetine was dosed for 14 days. But the paroxetine, per usual, was dosed in the morning.

DR. ROSENBERG: Dr. Ross?

DR. HERRING: Sorry. Just a quick comment also in response to your question. I think you were also asking about experience in the clinical studies in terms of interaction, just to clarify?

DR. MIELKE: Yes.

DR. HERRING: Unfortunately, we have somewhat limited experience in that we didn't have very many patients in the phase 3 trials who were concomitantly taking anti-anxiolytics to really assess efficacy, if I understood your question correctly.

DR. MIELKE: Thank you.

DR. HERRING: We also had some patients that were on antidepressants as well, particularly in the long-term study, protocol 9. And again, these were relatively small sample sizes, but we didn't

see meaningful differences.

DR. ROSS: Thank you. I wanted to ask about parasomnias. There were more abnormal dreams in the group on high dose suvorexant. I don't know whether those are nightmares. There have been reports of associations between narcolepsy and nightmares. Patients with post-traumatic stress disorder, of course, have recurrent nightmares and insomnia, and might well be treated with a drug like this.

Would there be any concern about a population like that?

DR. HERRING: We did see a few more of those types of events on drug, as you point out. There were relatively few events. Because the drug does have some minor impact on a REM stage sleep, it might be consistent with that type of profile. But these weren't particularly troublesome, and most of the patients didn't really discontinue due to these.

But your other question about the use in patients with other types of disorders like post-

traumatic stress syndrome, we just don't have any data around that at this point.

DR. ROSS: So were abnormal dreams nightmares, or not necessarily?

DR. HERRING: Well, in some cases they were reported as nightmares. And then for abnormal dreams, that's the limit of the information that we have regarding those.

DR. ROSENBERG: Dr. Morrow?

DR. MORROW: A quick question about the driving study. Did you have any measures of driving performance other than lane deviations? What I'm thinking about is, driving is essentially a multitask, a complex task, and people might control one aspect of performance like lane position and give up on speed control or threat detection. So it would be nice to have multiple measures of performance.

DR. HERRING: I'm going to ask Dr. Beals to comment on that.

DR. BEALS: Yes. The primary measure is the standard deviation of lane position. The standard

deviation of speed is typically collected; it's my understanding that that's a less reliable way to pick up residual effects in the test. Dr. Tom Roth could probably speak more to the limitations of the standard deviation of speed.

There are other information from the study overall. So, for instance, we used digit symbol substitution test and body sway and other things like that at the end. But that wasn't your question? You're more interested in the speed?

DR. MORROW: No. I was more interested in different ways of assessing actual driving performance.

DR. BEALS: Yes. Dr. Roth really should speak to the preferred ways to measure. But it is essentially the lane deviation measure.

DR. ROTH: This is Tom Roth. I can speak to the general literature. And in our review that we published, speed, standard deviation of speed, was significant in roughly 20 percent of the trials, while SDLP was significant in about 80 percent of the trials. So it just has much more sensitivity

than speed. But speed is affected in some trials, but a minority of trials.

DR. ROSENBERG: We will have one questioner, Dr. Voas. We're not going to have time for follow-up questions now. But in the afternoon, you're allowed to ask questions of the sponsor if they're clarifying questions relating to the discussion.

Dr. Voas?

DR. VOAS: My question is for Dr. Michelson. Do you envisage any recommendations to the users, the patients, with respect to use of any other substance or with respect to activities, having taken the drug?

DR. MICHELSON: Let me just make sure I understand the question. So you're asking, would we expect in labeling to have language related to the use of other drugs and to specific activities?

DR. VOAS: Yes. As you know, on standard for many drugs is to warn against certain activities, machinery and so on.

DR. MICHELSON: Right.

DR. VOAS: Or against combinations with like alcohol, other substances.

DR. MICHELSON: Right. So we would expect to have language that's similar to other hypnotics in terms of agents that could potentially interact with a sleep drug and that could have effects.

I can't give you the specific language here, but we would expect to have language around those kinds of things. And we would also expect to have language cautioning patients about behaviors that require attention, again similar to language that is generally included for other medications. We would propose that sort of language.

DR. ROSENBERG: Dr. Katz?

DR. KATZ: Yes. I had a clarifying question about the pharmacokinetic slide that we saw which showed AUC and, I think, C-9hours in obese compared to normal and then versus women. I don't know if we could have that slide up again, just -- I don't know the numbers as well as you do. But I just want to make sure I was reading it correctly.

DR. WRISHKO: Slide 1313, please.

DR. KATZ: As I read it, the AUC in obese patients compared to non-obese patients was about twice as much. I just want to make sure that I read that correctly. And there was no obvious comparison between, for example, the AUCs in obese women specifically versus non-obese men. There was a separate line for men versus women in AUC, but not something that combined obesity and gender directly.

DR. WRISHKO: Slide up.

DR. KATZ: So I just want to make sure that that was correct, and if it is correct, that there isn't one single comparison between AUC in obese women and non-obese men. Do you have a slide that shows that?

DR. WRISHKO: Slide up, please, 1304. So this is the table you're referring to, Dr. Katz --

DR. KATZ: Right.

DR. WRISHKO: -- in terms of the overall analysis based on both the phase 1 and then the phase 2/3 data, with the model-predicted AUC --

DR. KATZ: Right.

DR. WRISHKO: -- based on overall population of underweight versus normal.

DR. KATZ: Right. So obese normal is 1.6, and underweight normal is .78.

DR. WRISHKO: Correct.

DR. KATZ: So if you compare those two, that's twice. Right?

DR. WRISHKO: But the issue is that we actually believe that we should be comparing to the central tendency of our clinical experience for which, in this case, it's a normal population, 25 kilogram per meter squared.

Perhaps to more specifically address your question, female/male comparisons, stratified in terms of gender and across BMI, slide 1313 represents the box plots directly from the phase 2/3 data from the patients from which we had PK sampling. In here, we can provide some those direct comparisons. Slide up, please.

So with respect to the very furthest box plots on the right where we have obesity -- and this is stratified by gender.

DR. KATZ: Right, right. But this is C-9hours. I was looking at the AUC. Do you have --

DR. WRISHKO: This is C-9hour. We believe it is relevant based on the fact that it was direct sampling from the phase 2/3 population.

As I had suggested earlier, with the phase 1 model predicted values, there are restrictions in that the range of BMI isn't the same as what we had actually observed in the phase 2/3 trials. And we believe that that actually provides important information in making these assumptions and these analyses in ascribing this degree of change.

DR. KATZ: Right, right. I understand. You're right. You have objections to -- but I'm just asking, do you have or have you calculated -- even though you may think it's not necessarily the most appropriate way to look at it, do you have AUCs that compared, let's say, obese women versus non-obese men?

DR. WRISHKO: We have done those model prediction calculations. Perhaps we can get you a

slide after the break. But with respect to those, then when you compare again to the central tendency of female to male, you would get approximately 80 percent of an increase in exposure based on AUC on the model-predicted values, again with the assumptions that the model-predicted values may be more imprecise in providing estimates at the extremes of the BMI.

DR. ROSENBERG: We will now take a 10-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:50.

(Whereupon, a brief recess was taken.)

DR. ROSENBERG: We will now proceed with the FDA presentation.

FDA Presentation - Ronald Farkas

DR. FARKAS: Hi. I'm Ron Farkas, the clinical team leader for the Division of Neurology Products. I think first I'd like to thank also the committee for reading over I think what was probably more material than I had promised was

coming, and for coming today and considering all of these questions.

I think, too, it's important to say that the development team at Merck, we did work closely with them on this drug, and they really did an exemplary job of characterizing this drug. And we have a lot of data. There's a lot to talk about, and that's good, to have a lot of data. And we can't say that we have that for all drugs. And I think that we can use a lot of that data and figure out ways, I think, to benefit from the knowledge that was gained very carefully in these studies.

So maybe I'll actually go straight to this third question. And Dr. Katz made this point in his opening remarks. I think that in some sense it's the most important slide, that the approach that we are really trying to follow for insomnia drugs -- and it could be argued, of course, all drugs -- is that the lowest dose effective for the patient should be used.

It really does come down -- kind of the pun on gender aside -- to what dose would you want used

for your mother? What kind of information would you want behind that dosing decision? And probably to those who have listened to the news, we are working to apply this rule -- maybe a rule is the wrong word -- this very sensible, it seems to us, approach to all insomnia drugs. And of course, to make this work, there need to be dosage forms available for the patients to take that are safe and effective for those patients.

So then our preliminary conclusions, and I'll explain all this, is that suvorexant is effective but not safe at the higher doses mainly studied. The lower doses studied have similar efficacy and better safety, but the lowest dose, the 15 milligram dose, may not be low enough for safe use. The phase 2 data suggest 10 milligram may be effective, and less than 10 milligrams was not studied but could be effective.

I guess that I didn't really make this point in any of the other slides, but I think that we at FDA really like to analyze data, and we will analyze the data that we are given to try to figure

out what's going on. But I think that it's actually very clear, at least to us, without even all the fancy analyses -- and I heard that the sponsor was concerned about some of those. But I think maybe we should tread lightly on some of those analyses. They seem meaningful and suggestive, but perhaps, too, the most direct way to answer questions is to do it deliberately in a study designed to do that.

So certainly there could be, I don't deny, some significant uncertainty about some of our analyses; but of course, we have the opportunity to ask the sponsor to answer questions in studies designed to do so.

This slide is from an FDA document that tries to present a method for understanding how we make benefit/risk decisions, and it formalizes that thinking. I think that the FDA has always acted based on how drugs are actually used; not just if they're used perfectly according to the instructions, but how they're really used in the population. And with insomnia drugs, that seems to

be particularly important.

So I think through all of this, when we're thinking about risk/benefit, we're really struggling at FDA with what is a realistic instruction to give a patient? I don't want to get too far ahead in my presentation, but we were talking during the question-and-answer about patients who are sleepy and what they do when they're driving.

I guess that it's kind of a question to everybody. But have you driven when you felt sleepy? And that seems to be something that we all do because we have to get to work, and we have to get home, and there's so many things. And I think we're all sleepy sometimes. So this is really what that slide is trying to say, that we have to consider what these instructions mean and how could they be followed.

I think, too, that -- with a little more thought over the past few days, I think that -- so here I say a key safety concern is daytime somnolence can be severe and occur suddenly, and

that patients drive while impaired.

But I think there's a concern, and I'll talk about it in later slides -- there's something that's kind of impairment in the sense of ability to stay in the middle of the lane. But maybe what I should have underlined here or the word I should have used is that patients drive while they're at risk of falling asleep.

I think that in some sense, it seems, well, patients don't usually fall asleep while driving. But they do. They do. But I think what's more worrisome is that they have microsleeps, and they don't know they're falling asleep. And then can have multiple microsleeps that last for a few seconds.

So I think there's also been some comparison to other insomnia drugs already. And I think it's very difficult because there really is, plausibly, a very different kind of mechanism of action of suvorexant versus other insomnia drugs.

So just the comparison -- thinking about somnolence might not really be the right word. It

might be thinking about awake versus asleep, and that's in some sense -- that's the basic science understanding of orexins. It is a switch, and it's designed to act rapidly and completely so that you are awake one minute and you are asleep the next minute. And that's really, I think, the crux of the concern.

Then unconscious nighttime activity, which is sort of a mysterious beast, I should say. I'm not sure that -- part of the problem is that we never have large enough studies or enough experience to really know what happens, as you'll see later. But it's something that happens with other insomnia drugs, but we don't really know what. And I'll say later that we seemingly don't really know what is going on with this drug, either. And we've also talked about suicidal ideation.

Now, the other narcolepsy-associated events, I think we don't want to raise concern that suvorexant causes narcolepsy by causing an autoimmune death of cells that produce orexins.

But I think that it's helpful to keep in mind that what we're concerned about is something that's narcolepsy-like or even that's cataplexy-like. So it doesn't, I think, have to fit the exact disease syndrome to be a cause for concern.

This slide -- again, it was kind of touched on during questioning about which patients were studied and which patients weren't, and how much do we know about safety and perhaps efficacy in the real clinical population.

Certainly, there's nothing very unique about the suvorexant database in enrolling patients that are healthier than the clinical population. I think that when we see problems, when we see safety problems, then it just kind of brings to the forefront, well, what would the safety be in an actual clinical population? And I think that we saw that in this case.

There's the problem of concomitant diseases. And so certainly patients with obstructive sleep apnea, for example, have insomnia. And there was a question about that and it was answered with regard

to the apnea-hypopnea index, which is certainly important. But there's also that question of, well, in some large population, say, of OSA patients, what would happen with the combination of somnolence from the underlying disease with the somnolence from the drug? So I think that's a great concern. Of course, many, maybe even most, patients with obstructive sleep apnea are seemingly, to my knowledge, not diagnosed.

Then, of course, we had talked about use with drugs that are commonly prescribed in this population. And in particular, this is a recent number about the percentage of women who take antidepressants, and it gives pause for thought. So 23 percent of all women age 40 to 59 take antidepressants, and of course, as was mentioned, depression and insomnia commonly coexist. And that was very little experience with concomitant use of suvorexant and antidepressants.

Nighttime activity, getting back to the unconscious nighttime activity -- and there's a case I'll show later. But certainly, sleepwalking

is common in the general population, but to our understanding, patients with a history of sleepwalking were excluded from the suvorexant studies. And it's a concern about what would happen to those patients and concern about, well, how could you realistically exclude those patients from taking the drug.

So back to the narcolepsy-like events. I think that we truly don't know how to view the significance of these events. So there's one patient who reported weak knees when laughing, multiple times, actually. And this is a patient who had excessive daytime sleepiness. Well, we're asking the panel. We're asking the experts. But I think, to us, that looks like mild cataplexy.

The sponsor, I think, rightly looked at reports where patients hit the ground, basically, because that was where the clinical concern was. Are patients hitting the ground because of cataplexy? And I don't think they were.

But then looking very carefully through the adverse events for something like cataplexy -- and

of course, cataplexy is, I think, most typically mild. Cataplexy is something that patients tell their physicians about, and the physician doesn't even recognize that's what's going on. This can go on for years.

So I think that if it's of interest, we can talk about other cases. But I think to us they look like cataplexy. And I think, too, that it doesn't really need to look like classic cataplexy. Even for somebody with -- I'm losing the word -- narcolepsy. Cataplexy doesn't always happen with emotions. It can happen with surprise. It can happen for no reason. So I think there is some -- anyway, probably enough said about that. Nobody, we think, hit the floor, which is reassuring.

Sleep paralysis and hallucinations happened in about .3 percent of the population. And I think these are more concerning to us, although we're still not entirely sure what to make of these events. And so I put down a little bit of narrative.

So there's a patient, this first patient, who experienced sleep paralysis around the time of sleep onset, inability to move, as if someone holding her down; and then hallucinations, classic, really, for hypnagogic hallucinations, a sensation of an individual in bed with her.

From the narrative, we didn't really get a sense of the psychological reaction of the patients. But we think, or we're concerned, that these kinds of events are terrifying. It's terror that patients experience.

I should say that I had read about a patient with narcolepsy who was always able to go to sleep, but was afraid to go to sleep because of these hallucinations. And of course, narcolepsy patients can fall asleep. But we're talking about patients with problems falling asleep and anxiety about sleep. And it's not really clear to us, even if there's not physical harm from events like this, what we should make of this. And note that that first case was at 20 milligrams. The second case, I guess, is similar. But it illustrates it isn't

just this feeling like somebody's in bed with you, which is common, but there is really often a sense that somebody is going to hurt you.

The somnolence was talked about before, and I think you all saw the percentages. But I'd just like to -- well, let me -- I think the first point to make is that when we're talking about risk/benefit, I think we do need to think about how much harm, actually, the drug might do. And it isn't necessarily death, but we're treating a problem with sleeping, and the drug causes a problem with somnolence. And comparing these things, they're kind of in a similar category.

So it is saying something. It is something to worry about when we're thinking about insomnia medications that make people sleepier. And of course, it's dose-related. It's very clearly dose-related. And that would seem to suggest that we should really try to find the right dose.

Now, the excess daytime sleepiness, that's an interesting category because it is not severe somnolence. It's designed to be something else.

And I don't know that we really know what it is, but there were instructions given to the investigators to try to categorize or identify patients.

Again, I think that this was a great strength of this development program. And I think that these events could have easily been missed if there wasn't really focused effort by the sponsor to find them. And I would really caution, in any comparison to other development programs, that I don't think anywhere near that effort was taken.

But that said, this excessive daytime sleepiness was defined as something -- I believe I have the quote right. There's a longer quote; I don't want to get it wrong. But beyond potential residual drug effect, persistent recurrent impairing may be sudden and involuntary. So really, in a sense, it was pathological. It didn't really say that, but I think that's the only thing that the investigators could have understood it to be.

So this is the same patient who had weakness

in his knees when laughing. He was a 59-year-old man taking 40-milligram suvorexant. And the patient nodded off at a red light, had multiple episodes of nodding off while driving, one started to veer off the road until his wife yelled and he brought it back onto the road.

The investigator thought that the patient was experiencing microsleeps. And I think in some sense this is the driving study. This really points us in the right direction. Whatever doubt there is, we can talk more about what kind of driving study would be right, but this is real-world. And this is one out of a thousand patients or so.

But there were really other patients who might have been just like him, but you don't really know. That patient was really questioned in detail by the investigator. The patient had symptoms that were concerning, and the investigator took a lot of extra effort to talk with the patient about what was going on.

I think the investigators did talk to

patients, and I really do think they got a lot of information. So I don't want to say that there was any laxity about that. But still, some of these events are very difficult to capture because the patient doesn't know. And the wife isn't always next to the patient. So all of these incidences, well, that's the best that reporting can do. But it just might be the tip of the iceberg.

So about half of a percent of patients had excessive daytime sleepiness while driving, and it was described -- I think it's very troubling -- as starting while driving. You're already in the car. You just don't have much choice. You really have to keep driving. So that was one patient. Then the next patient, a different patient said, difficulty staying awake while driving. And the third patient said, need to pull over and rest while driving.

But pulling over and resting while driving is something that -- I mean, we live and die by the watch. Really, that doesn't seem practical. It wouldn't be surprising that patients just could not

be expected to do anything but continue driving.

Really, the characteristics of the events was just completely similar with placebo. Not only were there fewer events, but the quality, the events recorded for placebo, they were completely different, not really in the same category.

So the duration of somnolence is -- well, let me first explain, I guess, that this graph shows exposure over days, the days the drug is taken. And then each little line is the onset through end of the adverse event of somnolence for the patient. So the patients at the top had onset right away when they started taking the drug, and then the line ends when the adverse event ended. And patients farther down -- so these patients had onset at, whatever, 30 days. And there were some patients who had onset at 100 days, and whatnot.

So I think what this shows is that it's tough to know when somnolence is going to happen, and when it happens, it can last for a long time. But I think, too, the pattern of drug use for an insomnia drug, it isn't really like

patients -- well, I think, as Dr. Roth said, some points take the drug and then they keep taking it. And that's like how it's used in the study. But many patients take the drug for a few days or a day, and then stop, and then start taking it again. And we don't have that kind of experience.

So when we think about what day 1 means -- or maybe patients only have excessive daytime sleepiness on day 1. Well, day 1 is every day, every other day. It isn't something that -- you don't know what day day 1 is for an insomnia drug. So it's very hard to understand how we will deal with that in giving patients instructions.

Then in some sense it's clear from the examples that patients were unable to avoid driving while impaired by sleepiness in a clinical trial despite close clinical monitoring and warnings about possible impairment. And the warnings could have been stronger, and the labeling could be stronger, which is something that we'll talk about this afternoon. But I think that what was shown is

the ordinary warnings that the drug might make you sleepy or that you might be impaired while driving, well, operating heavy machinery; that those kinds of warnings are not effective.

I think that, of course, the FDA has and continues to use those warnings in labeling. But I think we are understanding now that patients are not reliably aware of drug impairment. They're not reliably aware of the consequences that come from being sleepy.

So this was mentioned before. Maybe they know they're sleepy, but how sleepy, and what's going to happen to them? What are the consequences for that patient? I don't know that any of us -- we know that we're not so aware when we're not aware.

Again, this is just the same type of data, recent data. Dr. Roth was the co-author. "Drivers can poorly predict their own driving impairments." Anyway, that's the bottom line. And the advice is to label, or if you give a patient advice, that they should listen to their body and not drive if

they feel their driving is impaired. It should not be relied on because patients may not be aware of their driving impairment.

I should also make the important point that if half the patients are aware of their impairment and half are not, you really have to be concerned about the half that are not. And I'm not really sure what that percentage is. But even if 90 percent of the patients were aware and didn't drive, what about the other 10 percent of the patients? And how many patients is that, and what's going to happen to them?

That's really our typical way of looking at adverse events. We don't look at the average liver injury in a population; we look at the patients with serious liver injury. We don't really think that we should look at the average of almost anything with adverse events.

This point came up before, too, what about discontinuation? And we saw, and I think the sponsor said, that discontinuation was infrequent even in patients who experienced somnolence or

excessive daytime sleepiness, and also excessive daytime sleepiness. And that seems like it's a safety problem. It seems to be saying that patients cannot self-identify, they can't be expected to self-identify, that the patients who at risk will keep taking the drug.

A bit has been said about the formal driving study. And I don't think I'll repeat this except to say that what's legal for driving and what's illegal, I think that matters. And the FDA is not police officers on the street regulating intoxicated driving. But we think that matters.

Even the weaving itself, this weaving in the lane, that is what law enforcement officers are looking at, often, when they're looking to see if somebody's impaired by a drug. They're looking at something that looks very much like this test of driving. And we don't know -- this came up before -- we don't know the correlation between weaving in the lane, in the driving lane, and crashes. But I think, from looking at manuals for police officers, that that's what they're looking

for.

I should note, too, that this .05 percent blood alcohol, I think that we at FDA view that as a pretty -- I'm not quite sure if the word is conservative or anti-conservative -- level. That is about the blood alcohol level after having three drinks for a man, three standard drinks.

Again, it's pushing up against that what is a crime to do? We're not even in that range of what's unwise to do. We're really trying to say what's -- we're trying to prevent criminal prosecution of patients taking their drug as prescribed.

This just illustrates to us, I think, the face validity of the SDLP, that there's a path you need to follow, and it's a problem if you have difficulty following that path.

Then, again, as was touched on already, there's really a very serious question about if that was the right test to pick, and the FDA, we asked for that test. But I think, in hindsight, we don't know if that was the right test of driving

impairment from this drug because the basic science tells us that this drug acts on the switch between wakefulness and sleep. And the SDLP doesn't measure that. It doesn't measure the risk of falling asleep or microsleeps.

It's still useful because being sleepy does impair performance. And the test was positive for suvorexant. But again, there were four patients who stopped the driving study because they felt somnolent. Of course, again, how many patients didn't stop their driving test who probably should have or maybe should have? I think that's one question.

But I think, anyway, I guess the point is clear that there are ways to study risk from falling asleep, and that wasn't done for suvorexant, and maybe it should be.

So this is, again, a point about how to identify a safety risk. And the primary endpoint that the sponsor had selected for the driving test was the average impairment of all patients. And I think that can be useful, and the average

impairment did worsen. I think it's something to consider.

But when trying to think about adverse events or a biomarker of an adverse event, if that's what we want to call this, we're really interested in doing an outlier analysis. Just like if you're taking a look at liver injury, trying to predict liver failure, you're going to look at the individuals who have elevated liver enzymes and not at the average.

I think that even the test that we picked, even the statistical test that we picked, which was looking at the imbalance between people who got better and worse, didn't even full capture what can be seen in some of the graphs about how much worse some of the patients got.

So this is the results, the statistical results. And so for the symmetry analysis, which again was explained a little bit by Dr. Katz, and I'll explain a little bit more in a minute, the test was positive for impairment on the first day, first day after treatment, for as low as 20

milligrams in adults. That's really something to think about. That 20-milligram positive study is a concern for us.

Now, in the elderly, there were 24 patients -- and again, I don't want to be accused of not liking other people's leans and saying that this is a lean that the FDA likes towards statistical significance. But I think that there is an extra moment of pause when there's a lean in a safety test versus a lean in an efficacy test, and especially when studies are very small. This is a 24-patient study. The 30-milligram was leaning towards significance in the elderly.

I think that a lot of the slides that follow are our best analysis of data that was not designed to be analyzed in this way. So I don't want to try to say that we know what's going on. But we're trying to explore what might be going on with this.

When we take a look at the symmetry analysis -- I should show it; here -- when we take a look at data like this, we say, well, okay, it was statistically positive. That's all that it was

really designed to detect. But how many patients got worse?

This is the adult driving study this first day after drug. And about 20 percent got worse and really none got better. So anyway, it seems to us reasonable to, at least as a hypothesis, think that 20 percent of adults might be impaired after the 20-milligram dose.

So while I have this slide up, I should finally get to explaining the symmetry analysis. So there is noise. There's a substantial amount of noise in pharmacodynamic tests. And the symmetry test is designed to account for that statistically.

You take a look at the people who got much worse, at a level that you set as a level of concern, what you think is much worse, versus the number of patients that got much better by the same amount. And if there's more that got worse than got better than can be explained by chance, that's a positive signal for impairment. It's really that simple.

So in the elderly driving study -- let me

just bring that up -- there was not impairment at 15 milligrams. That's something that can help us try to figure out what's safe. We don't dismiss it at all. But it's kind of obvious -- and I'm going to go into a really complicated slide to talk about 15 milligrams versus 20 milligrams -- but 15 milligrams and 20 milligrams are really close, and you don't really need to think too hard about that to know that some patients who take 15 milligrams are going to have exposure to the drug that is exactly the same as patients who take 20 milligrams.

I think that, again, all the concern that we're talking about with what dosage form is available and who needs what dose is that we can talk about exactly which patient subgroups need exactly which dose. But there are identifiable people, a lot of identifiable people, who we know will have exposure from the 15-milligram dose that looks just like exposure from the 20-milligram dose, certainly.

We think that by some metrics it looks just

like exposure from the 30-milligram dose. There's already been this discussion about AUC versus blood level, but we've analyzed this, and we I think are about as certain as we can be that exposure is higher in some patients even though they got the same dose as some other patients.

So this is where it gets a little complicated. And I'm going to go through it a little quickly because this is all kind of obvious and I already kind of said it. But we do think that somnolence increases with exposure. So here I'm leaving dose for a second. Let's not think about dose. Let's think about how much drug is in that patient. And the amount of drug in the patient matters just as much or maybe more than the dose.

So this is the slide which, in hindsight, very complicated. But I think I've really already said it, and that is that if you take 15 milligrams, you're going to have lower blood levels than if you took 20 milligrams or 40 milligrams. But some patients who took 20 milligrams or 40

milligrams, they had blood levels like you do from 15, and they were impaired on this test.

So we can match -- and again, there's a lot of noise here; I do not deny that. But from the data that we have, we have concern. That's definitely not proof, and maybe the evidence isn't really strong, but there is definitely reason to be concerned that people who take the 15-milligram dose have exposures that have been shown to impair driving.

Again, there's a lot of noise. But isn't just 2.5 centimeters. It's 4 centimeters. That is what people think the impairment is from driving at .08 blood alcohol, or perhaps it's even higher, more impairing. And when you get above the 5 centimeters, like in that diagram before, some patients are really going to be starting to go outside of the driving lane.

So then we get into the area -- I'm going to go to the next slide -- where we don't have very much data, and that is what happens to patients at night, and in some sense, what happens to patients

at night when nobody else is around, or when the people around are sleeping.

So this patient was in the PSG lab, and there were people awake and watching. And 2 and a half hours after dosing, he started talking in his sleep, sat up in bed, and then went back to sleep. But then after that he lunged out of bed -- this is the quote from the study report -- "and hit his head and face against the wall." That's all we know. That's all I know, and I don't think the sponsor knows more.

Then the patient had a sleepwalking event two weeks off the drug, which tells us, perhaps, something about the patient. I'm not entirely sure how to use that. And the patient had a past history of sleep talking, not sleepwalking.

So patients who were at risk were excluded. There was an attempt to exclude patients at risk for this kind of behavior. And this patient got in, and he had this event. And I think that maybe it's pointing out the obvious, but while nothing so bad happened to this patient, but it kind of

depends on how hard that wall is. And it kind of depends on if there was a coffee table where he was lunging. So I think it's very concerning.

Then we really have no -- I mean, it could be argued that with this few events, we don't really know that it's drug-related. But that's not really very reassuring. We don't see events like this very often. I mean, I don't ever remember seeing one. And again, it's not often collected as well as it was in this development program. But it's hard to know what to think about this.

I tried to give it a name. And I don't want to put too much emphasis on that, but it looked to me, at least, to be something that might fit with REM sleep behavior disorder, which does occur in narcolepsy, characterized by intense motor or verbal paroxysmal dream-enacted episodes. Individuals act out dreams, sometimes with serious injury to self and others. But perhaps that's even distracting, and we can talk about what to do when an event like this occurs and what to think about it.

There was one case of sleepwalking. Again, nothing serious happened to that patient, but I think we've learned from other sleep drugs that patients can get into trouble when they are out of bed and unconscious. It kind of is obvious.

We really worry about the incidence of that. And we think that with other sleep drugs, it's really rare, and we shouldn't be seeing it in drug development programs. We shouldn't be seeing it in a study of a thousand patients. And if we do, we don't really know, but if we see it in a drug development program, then we guess that it might be happening more frequently than it happens from the other sleep drugs that are approved, where we know it happens.

The suicidal ideation was mentioned, and I won't go through the details, but I think that the FDA agrees with the data that was presented before. There was an increased amount of suicidal ideation, particularly as measured with this questionnaire, in patients at the high dose.

At the low dose -- boy, there's a number

that -- the number of .2 percent in low dose versus .1 percent in placebo. Well, it's hard to know if that's real, that's true. There's only one patient in each group, the low dose and the placebo. But it's hard to know if that's reassuring or if that's not reassuring. We mostly just don't know.

Now, we do think that suicidal ideation, or an increase in suicidal ideation, increases the risk of suicide. So it's hard to know how reassured we can be that the suicidal ideation was mild because again, we're trying to count adverse events, and adverse events are things that happen to individual people.

I don't think it's very reassuring, too, that this happened in patients who had or generally had a prior history of stress or ongoing psychosocial stress. I have stress right now, so I'm not very reassured. But even so, there's a lot of patients with stress. And I think all the data, still, even if you were only worried about people who experienced increased suicidal ideation who had baseline risk factors, that's still a lot of

people, of course, and a lot of people with insomnia.

So then to efficacy. I'm going to talk a little bit or get into discussion about subjective versus objective endpoints and whatnot. But in some sense, I think that we really need to keep track of the bigger picture, that high doses of many insomnia drugs will lead to patients sleeping more and will lead to patients sleeping faster. And that's not really what we're trying to accomplish. We're trying to accomplish patients getting symptomatic relief, getting objectively longer sleep, and doing so safely.

So I really think that a lot of the discussion about higher doses might be more effective or are more effective by certain measures, it's the wrong question. And you could say that about any drug, or any sleep drug -- maybe not any, but many, certainly. Yet I don't think that we would just keep pushing up the dose of these other drugs. It would hardly enter the discussion.

So it's then back to objective versus subjective endpoints. And I think that we struggle at FDA with trying to understand what is important benefit in insomnia. And we have PSG. We have objective data, which to us seems very basic, that if a drug is prescribed to increase the amount of time that you sleep, we would like to show, or have the sponsor show, that it increases the amount of time that a patient sleeps.

The subjective perception of sleep is really a far less obvious endpoint for trying to understand what's important to patients. It is important, and we do pay attention to that. But the fact is that everybody knows that sleep interferes with your ability to know how much time you've slept. It's just not a reliable endpoint. And then when trying to weigh risks against benefits, it's just very difficult to know -- I mean, it's already difficult to know what to think about a five-minute difference in polysomnography. But it's really difficult to know what a five-minute difference in subjective sleep is when it

didn't happen.

The second bullet here goes into -- well, back to the first bullet. Sorry. Well, the drug -- I said -- well, okay. People have poor perception of how much time they've slept ordinarily, and then when you add a drug, of course there could be more misperception of sleep time.

I think one concern that we have, and we can discuss this afternoon, is that actually patients might report longer sleep due to an adverse effect of the drug. So you can't report how long you were awake at night if you don't remember.

Is that a benefit? Well, not remembering is usually adverse. Certainly not remembering some unconscious activity that you did out of bed, that's adverse. We certainly think that happens from some sleep drugs. So how do we interpret an endpoint that could represent both benefit and harm? So again, it's potentially meaningful, but it has to be interpreted -- again, the subjective sleep time really has to be interpreted with caution.

Then the effectiveness of the 10-milligram dose. I think there are some slides coming up that are pretty fancy, but if we could just focus on the primary endpoint of the phase 2 study that was positive for the 10-milligram dose for sleep efficiency. I put here that it's for sleep maintenance. But I think that's actually perhaps a misleading word. The FDA is very focused on sponsors showing evidence of efficacy for exactly what they're claiming and labeling, and so we spend a great deal of time thinking about sleep onset versus sleep maintenance and latency to persistent sleep versus wake after sleep onset.

But the 10-milligram dose was effective for sleep efficiency over the whole night. And then if you look hour by hour, at night 1, which we'll talk about a little bit later, it was not as effective. But these drugs have a long half-life and reach a level. They build up.

If you take a look at week 4 hour by hour, the 10-milligram dose and the other doses, they were overlapping, hour 1, hour 2, hour 3,

throughout the whole night. So I don't want to mislead that somehow there's something only going on with sleep maintenance like with early morning awakenings or something at 6:00 or 5:00 in the morning. It's really throughout the night.

So I think we have a high degree of confidence that 10 milligrams works. And then when we're talking about works, you have to consider what the patient wants. And I think we're really convinced that there are many patients who want that kind of effectiveness.

So then into the finer points of the analysis, and that is that -- well, study 6 was small, and there's noise. There's a lot of noise involved in these studies. It was pointed out with, I think, study 29 that study 9 high dose missed the latency to persistent sleep endpoint at 3 months, I think. And that's a study that's, I think, something like ten times larger than this study.

There is noise. There are other effects in these studies. And I think that we really tried

to consider all the data and not just look at the p values. So we didn't really raise the question of, oh, well, there's one data point in the very large study that wasn't positive because I think we have confidence.

I guess that's the thing. We're looking at all the data. We're looking at all the efficacy data, and we're trying to use that to figure out what works. So when we do that with study 6, I think we feel secure. When a drug has been shown to work, we feel secure in our search for dose-response to look at endpoints that weren't prespecified, to try to understand if there were some things that were irregular in the data. Again, it's a guess, but things that maybe we could analyze to try to understand what happened.

For study 10, when we do that -- not by all analyses, but by some -- it looks to us that the 10-milligram dose works for latency to persistent sleep, and even that it works for latency to persistent sleep on night 1 in addition to week 4.

But again, I think in hindsight this is

perhaps over-analyzing. And it works for sleep efficiency, which was the primary endpoint. And I think the other thing is that we do have the opportunity, if we don't believe these analyses -- and if we think it's important, if the committee thinks it's important -- to ask the question in a study designed to answer the question. So we don't just have to depend on the data we have. It depends on what's -- or if other data is important to get.

This really shows the same data. And again, this is -- well, I kind of skipped over, and I can explain more; I don't want to cause confusion. We were concerned about period effects. It was a crossover study. We were concerned that patients treated with drug in the first period had effects from the drug in the second period.

So this slide shows, and the previous analysis shows, our analysis of the first period, which is a completely reasonable post hoc analysis to do when you're concerned about a carryover effect.

Anyway, this slide really just shows what I had said before, and that is that the dose-response looks very flat. There's a lot of noise. It looks very flat. And we don't think we know what happens between 10 milligrams and zero. There might be -- maybe the next point is going to be here. Maybe the next point is going to be here. We don't really know. So we tried to do some analyses to clarify that. And again, they're exploratory.

So you can take a look at, again, the exposure that people get from a set dose, from a fixed dose. So if you give patients 15 milligrams, some will get a high exposure to the drug. Some will get low exposure. And then you can ask, well, the patients who got the low exposure -- this is AUC -- they're kind of a stand-in, I should say for patients who could have been given the 10-milligram dose. And you ask, did they have the same efficacy as patients would have who might really have been given the 10-milligram dose?

I hope I didn't say that too unclearly, but anybody who doesn't understand can ask me during

the clarification, or during the questions. But basically, it's trying to recreate from a series of doses what would happen if you gave patients a lower dose. And I think the bottom line is that we don't see a clear diminishment of efficacy at these lower exposures.

This is sleep maintenance. These green ovals just highlight again that this is the exposure that would be seen from the 10-milligram dose. And from this kind of analysis, it looks like it's effective. Again, it's a post hoc analysis, but it suggests that it's effective.

The same thing was done for sleep onset, and there really isn't evidence of diminishment of efficacy at the lowest exposures. And again, the same, similar, the green ovals show or highlight the exposure that you could expect from the 10-milligram dose.

So this is a complicated slide that's probably worth talking about in some detail. Suvorexant has a 12-hour half-life. So when you wake up in the morning, more than half of the drug

is still in your body. Well, of course, what really matters is the effect that that drug happens. And you don't really know the effect of a drug or drug level during the day versus at night. There's circadian rhythms that were talked about.

But I think we're going into this analysis of blood levels during the day knowing that there is a really large signal for somnolence and excessive daytime sleepiness. And there's certainly reason to be concerned that the blood levels that are present during the day are causing patients to be sleepy during the day.

So from the 40-milligram dose, a single dose, there's exposure to the drug in your blood the next day that's as high as the maximum blood level from the 10-milligram dose. And we think that's effective. But if you keep giving suvorexant, because of the 12-hour half-life the blood levels increase so that -- and it happens a little faster than this, but after a few days, when you go to bed, you already have an effective blood level before you take the next pill, just as you're

going to bed. You've got an effective blood level from several days past. And now it's night, so you think, yes. After a few days of this blood level building up, you have an effective level even before you take the next dose.

Then, of course, the next day when you wake up and go about your business, your blood level is even higher. It's as high as the maximum blood level from the 15-milligram dose, and the 15-milligram dose was very clearly shown to be effective in the larger phase 3 studies. So that certainly seems, on face, very concerning.

So getting back to -- what do we have to work with, with this drug? What can we think about to try to figure out how this drug can be used safely and effectively? Efficacy for sleep latency depends on you taking the drug, the drug going to your stomach, the tablet breaking up, being absorbed, and the drug getting to your brain, basically. And that takes some time.

So the Tmax for suvorexant, as mentioned before, let's just say it's 2 hours. Well, most

patients, even with insomnia, are asleep by the time 2 hours comes. And of course, it isn't so that the drug only works at its highest blood level. It can work before that. But basically, it takes time to reach an effective blood level for sleep latency.

So it's not really unexpected that if you take a 10-milligram dose, the efficacy on night 1 -- I think in particular the first few hours of night 1. Maybe let's just focus on the first hour. The drug is not rapidly absorbed. You're starting from zero. And your blood level is not going to be very high.

But one way to approach this kind of issue -- I think there's two ways. One thing I think to consider is, in the risk/benefit profile, we can talk about the importance of efficacy a half-hour after you take the drug. That is important, and it does have to be weighed against safety. I think there is reason to believe that a high dose will reach an effective blood level on night 1, starting from zero, faster than the low

dose. But then maybe there's ways to get around that, too. We have other drugs that we recommend are dosed up to half an hour before bed.

We're trying to analyze this now, but I think we do agree, or at least our initial impression is, that there is not that much impairment on like the DSST, which some other drugs seem to impair more. So maybe it would be safe for the patients to take the drug a little bit before bed, especially on the first night. And then the blood level from the lower dose is going to be effective by the time they go to bed, and the drug would be more effective starting from day 1, even at a lower dose.

We already talked about special populations. And I think that -- the first thing to say is that just yesterday, I got another analysis from Dr. Dimova from clinical pharmacology, and she said, tell them its twofold. We think it's twofold, not two- to threefold.

So for AUC, for the exposure to the drug, our analysis now shows that it's twofold higher in

women versus men. The FDA and the sponsor were discussing how to measure increased blood exposure. And there are different ways to do that. You could measure the blood level at one individual point, which seems to minimize this increase. You can integrate over the whole 24-hour day for AUC for drug exposure, and then that adds up to twofold higher. So really, it's the same measure, or it's the same elephant, just different ends of the elephant.

Then when you're thinking about what dose to give, sometimes we can tell patients, well, don't take this drug. We don't have a dosage form that's safe for you. But when we start talking women who are obese women, that's the target population. So it doesn't seem reasonable. I have to be very careful when I say things like that. But it's a large part of the target population, and it doesn't seem realistic to try to write labeling around that.

Then there's all sorts of other reasons that patients have higher drug exposures. There are a

lot of interacting drugs that inhibit the enzyme that metabolizes suvorexant and leads to higher blood levels and leads to higher exposure. And it really is unrealistic that patients aren't going to ever take these drugs or take these drugs all the time with suvorexant.

Then there's simply patients -- there's always patients who get a higher drug exposure than average. That's what it means, who are more pharmacodynamically sensitive than the average patient. When we're thinking about safety, we should really think about those patients, too. There are patients at the upper end of the exposure from a given dose who really should use a lower dosage form.

Actually, this slide, there were a couple emails that came from Dr. Dimova. And they've been working very hard, and I partly didn't understand, too. But I think this is actually an error. There's always been an error in our thinking about elderly versus adult.

To my understanding -- and if there's any

clarification question, it will have to go to her -- the 15 percent was a number that came out of the phase 3 studies, and we think that it has other factors besides age in it. I think weight, their obesity, is one of the biggest factors. I think I got that right. So actually, the age effect is smaller than that. But again, I think that's probably a detail.

Also, when we think about a dose adjustment being necessary in the elderly -- well, the elderly had fewer somnolence adverse events than the adults. I'm not really sure what to think about that. There's been some talk about that. On one hand, less somnolence as an adverse event might be real; on the other hand, it's a different population, and it might be the same amount of objective somnolence, if I could mix metaphors. But it's reported less in the elderly patients, so it might not be that reliable.

But perhaps what is more reliable is that in the driving study, the impairment in elderly for 30 milligrams was very similar to the impairment in

adults from 20 milligrams. And the baseline SDLP was very similar. It was a little bigger in the elderly, but it does seem to provide both subjective and objective evidence that the elderly are not more sensitive, and they might even be less sensitive, to suvorexant. Also, there's a couple of slides coming up -- I think we find that the exposure-response relationship is similar, too.

Now, this slide again seems important when we're thinking about the dose that women need. So we can argue about how to measure the higher exposure in women. It is surely higher in women, though, whether measured by AUC or by blood level at each time point. But it does seem perhaps very real that the incidence of somnolence was higher in women. They had a higher exposure, and it wasn't just a little higher at the low dose; it was three times higher.

Well, it depends on how you look at it -- if you look at the placebo, maybe women even complain less. You don't really know. It might be noise. It might not be reproducible. But it really looks

like women were more severely affected by the same dose, and that's a great concern. We really need to provide dosage forms that are safe and effective in women.

Anyway, this again might be belaboring the point, but we think that the exposure-response relationship for sleep maintenance and for sleep onset are similar for adult and elderly. And this actually might be helpful. I think that the sponsor was very wise in testing four doses, four different doses, two in adults and two in elderly. And I think we're trying to use that to figure out what a safe dose is, trying to figure out if adult and elderly patients are similar, if information from one population can be used for another. So I think that we're hopeful when taking a look at the exposure-response relationship from adult and elderly that it's similar enough to draw conclusions from one group for the other group.

Then back to benefit/risk. We talked about some of the weaknesses of a patient's perspective of the minutes slept. But the FDA, I think, has

always tried to be focused on benefit to the individual patient, and is even more focused on that now.

One endpoint that we don't ordinarily ask for, for an insomnia drug, but that seems important is daytime function, subjective daytime function. We kind of have objective daytime function from the driving study, and it was worse. Of course that's a concern.

But then taking a look at subjective daytime function, we talked briefly before about the Insomnia Severity Index and the score on that, and that improved with drug. The Insomnia Severity Index incorporates questions that also measure, maybe a little indirectly, a patient's perception of the amount of time that they slept. But there's one question there about daytime function that perhaps is influenced by how much time patients slept, but it doesn't ask about that. So perhaps it's measuring a different axis of benefit.

I think that what we saw, we did see benefit, but it was modest. And what really struck

us was that between baseline and the month 1 measurement, there was a tremendous amount of improvement for patients on placebo and 20 milligrams and 40 milligrams. So it was time. It wasn't the drug.

This is not to say that the drug isn't working. There's certainly evidence, at the less severe amounts of interfering with daily function, that the drug has benefit on this endpoint. But we're trying to figure out how to weigh the benefit against risks like car accidents. And so it seems important to take a look at, really, the details of the kind of benefit.

So patients who have more severe interference with their daily function, perhaps we should look more closely at those patients and maybe a little bit less at the patients who have a little or not at all. We don't disregard that, of course, but maybe when thinking about risks and benefits, we should take a look at patients who have much or very much interference with their daily functioning. And perhaps there was some

benefit from the drug, but it was just very slight. And again, that's something to talk about this afternoon when we talk about risks versus benefits.

So just to recap what the FDA is concerned about, daytime somnolence, impaired driving, unconscious nighttime behaviors, suicidal ideation, and narcolepsy-like events or syndrome. And putting all this together, our preliminary conclusion -- and it is preliminary; I should stress that -- is that 30 and 40 milligrams seem unsafe; the 20-milligram dose impaired driving in adults. The 15-milligram dose, as I said before, it's pretty close to the 20-milligram. And in some patient populations, some key patient populations, the exposure from 15 milligrams is certainly as high and really higher than the exposure to the 20-milligram.

Then if you start adding together all the different patient populations that might not have a safe and effective dose in the 15-milligram, it starts to almost look like the majority of patients because there are obese men, pre-obese women,

concomitant drug use either inhibiting cytochromes that metabolize suvorexant. There's pharmacodynamic interactions. So suddenly, the number of patients who might have safe and effective use of the 15-milligram dose, this gets smaller and smaller. And again, the adverse effects seem to be clearly dose-related.

This next bullet point, "Patients can't reliably respond to their own risk from drug," well, I think that that covers a lot of adverse events. It covers driving. It probably covers suicidal thinking, too. And "Respond" means both detect and then do something about it. We saw that patients thrive while they're sleepy. They don't discontinue drug when they have adverse events. So there's really a lot of problems with relying on patients.

You kind of need to engineer in -- and I'll use the word "engineer" even though we have an engineering professor on the panel. I think the key thinking is that we really want to engineer in some safety. And that is, again, referring back to

one of the earlier slides when we have to consider real-world use. We're trying to engineer in enough safety so the drug can actually be used safely.

Then there's the no clear efficacy decrease down to and including 10 milligrams. And we think that the risk/benefit balance might even be better if less than 10 milligrams was studied. Of course, we don't have any data about that. But I think the panel should still consider what it means not to have that data. And of course, we're here to think about what data is necessary to have, even what data we might still need to get.

Then this other last bullet, again, to us it seems very definitive. But to us, we can't really think of a justification for using higher doses of an insomnia drug than necessary for efficacy. That is in some sense a very fundamental statement of safety and of the goals of medicine.

Also, just to repeat, all of this data is collected in a population that was healthier than normal. And so somewhere there has to be built in, I think, a consideration about what might not be as

safe in a real population.

I think this afternoon we're going to talk about the practical way to look at risk. Some events are very rare; so for the traffic accidents, I had a slide about traffic accidents, and it didn't look very different between the drug and the placebo, although it's not maybe totally unnotable that there were more violations and maybe more accidents with the drug.

But those aren't really the events that we're interested in. And the traffic accidents that we're interested in are uncommon, as traffic accidents go. They're not that uncommon, and that's part of the reason that I put up this number.

So there's 33,687 deaths from motor vehicle accidents. Well, that seems like a lot. It surely is a lot. But there are -- I think the number is 6 million traffic accidents every year. And we didn't see any traffic accidents that caused death in the development program. We didn't see any traffic accidents where we think a patient fell

asleep and drove off the road.

So we just don't know. We don't have any information about the events that we're interested in. And it's really not very easy to get that data, especially when you're concerned about a small percent increase in risk. That's again where these numbers come in.

So designing a study that really measured deaths -- well, I don't know what percent increase in deaths we're interested in. Maybe it's 10 percent. Maybe it's 5 percent. Maybe it's 20. I don't really know. But surely a 10 percent increase in deaths when there's 34,000, that's a meaningful number. And so it seems worth it to us to try to use perhaps imperfect methods to figure out if that's going to happen.

Again, it's extremely difficult to even consider designing a study, an actual study, where you would demonstrate that more people were killed using a drug. How could you do that?

Suicide is really the same thing. Suicide now, there's more deaths from suicide than there

are from motor vehicle accidents. In fact, we have as our concern today two of the leading causes of death in healthy individuals, otherwise healthy individuals.

So a very small increase in the risk of suicides, that's many people. And I think that's why I put the number there. It just is very difficult to know for sure. It's very difficult to test. But when we have data that shows this might happen, this really gets to the lowest bullet point here.

We're not even necessarily saying we haven't decided. We're not necessarily saying we can't approve this drug. But I think the key message is, is it worth trying to make it safer? How much is it worth to try to make the drug safer? How many people are you willing to risk versus how much effort are you willing to take to find the lowest effective dose for each patient?

That's all. Thank you.

Clarifying Questions

DR. ROSENBERG: We have 15 minutes for

clarifying questions. I'd ask people to limit themselves to one question and make sure it's clarifying.

Dr. Rizzo?

DR. RIZZO: Dr. Katz and Dr. Farkas underscored the need to evaluate efficacy of therapy in the real world. What strikes me in the case of this drug is that there's an opportunity to measure real-world sleep, but I'm not sure that was an outcome measure in any study of this drug, say, with accelerometer watches at night.

DR. FARKAS: Well, I think that we've -- we're not sure that we have the best measure of sleep for these drugs. And maybe we could even talk during the discussion period.

I don't think there was any accelerometer data here. It would be, I think, maybe important during the discussion to hear why you think that is, what other information that would show us.

But if it's answering your question, I don't think we know the best way to measure efficacy. We've been using PSG because it seems, on face, to

measure how much time people sleep. Perhaps it seems to measure sleep more precisely, accurately, even, than an accelerometer, too.

DR. RIZZO: In a similar vein, you mentioned the importance of awareness of impairment. But I'm not sure that you've given any advice to the sponsors on how to measure that.

DR. FARKAS: Well, I think, getting back to trying to engineer around that, that we think that the way to approach it is to try to minimize the risk. So there will be risk. Patients will be unaware of their impairment.

I think that probably some patients will drive who should not be driving, and some of those patients will crash. But the goal, really -- the first goal, I think, is to try to minimize the chance of that happening. And one way to do that is to have people use doses that are less likely to cause that.

Then at some point you get into a situation where you think there is some irreducible number of traffic accidents or some irreducible amount of

harm from a drug, and then it really is -- we don't really like using the scale or the balance analysis, but you have to decide if the benefit from the drug is enough to outweigh the risks, and you can't reduce the risks any more.

DR. ROSENBERG: Dr. Chervin.

DR. CHERVIN: Thank you for a very thorough analysis, but it does leave me with some questions.

You raised and focused on the risks of suvorexant. But do you to some extent consider what the patients are doing if they don't take suvorexant? I think many patients might take other hypnotics and have worse, perhaps, for all we know, outcomes, as perhaps even suggested by the positive control in one of the studies, in the driving studies.

How do you factor in what they're doing if they're not taking suvorexant?

DR. FARKAS: Right. I think that's a great question, and it really is something that we are working on as quickly as possible every day. But I think that we have recently changed dosing of

Ambien and Ambien CR. And we are trying to apply this approach to all insomnia drugs, those that are approved and those that are not approved.

I think that I'll maybe go out on a limb a little bit and say that I don't know that you were exactly implying this, but I don't think that we can approve a drug that might not be safe because we're dealing with something that's on the market right now that we're worried about.

DR. ROSENBERG: Dr. Cohen.

DR. COHEN: So being close to elderly, I will try to go very quickly. In clinical medicine, most of my patients are at least on five medications in the elderly class, present company excluded, and also self-medicate, by the way, for sleep with alcohol and also antihistamines. But more important, in the studies, you're treating a disease that presumably people aren't functioning well. And they're tired during the day, and they have excessive daytime sleepiness.

Why in the analysis is that worse with study drug than placebo? It doesn't make sense to me

unless there are these alternative therapies that they're doing.

DR. FARKAS: Well, I think there are questions completely beyond my expertise about what insomnia is, what problems it causes. I mean, I try to learn from the experts. We all do. But I think that there is significant disagreement among insomnia experts about what should be treated and how much and when.

I was reading a paper from 40 years ago about insomnia treatment, and the investigator was saying, it's good to have next-day residual effects from benzodiazepines because it sedates the patient. Well, that was the view 40 years ago. So what are we trying to do now?

I think we're trying to do something different. We're trying to have patients perhaps function better the next day. But we don't have that as an endpoint. We still -- well, we wrote our guidance in 1974 for insomnia drugs. We need to get to that.

Your question is very fundamental. What are

we trying to treat? Obviously, a lot of sleep drugs increase somnolence the next day versus other patients with insomnia. Right? It isn't like patients with insomnia have somnolence and it's somehow being decreased but there's still some left. The drugs are increasing somnolence. They seem to be causing that harm.

So again, it's really just a fundamental question of what the disease is. Is it during the night? Is it during the day? What's the relative importance? What are we trying to treat? What adverse events or effects do we think can be accepted and which are not acceptable?

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: You know, there are things that are known. For example, you have a ceiling effect when you have a driving simulator or you drive. So when you find some differences as you presented, they don't make any sense to emphasize because you have reached a ceiling effect.

The second thing is when you talk about one

case, your drug company could have given you more information. You could have resolved if that person had REM behavior disorder or not. That's data. And to sleep talk in a chronic basis and abruptly sleepwalk doesn't make any difference. It's parasomnia, and the patient had the parasomnia.

So I think that we should not take independent cases like that to make conclusions. My major concern is what has been expressed. Patient insomniacs, if you give a very low dosage, are going to take a second dose in the middle of the night. Okay?

So we have no information of what's the somnolence when you give the drug, how it decreased during the night. And if we are going to have to select the lowest dosage, we have to select a dose which will be sufficient for all the maturity of the insomniac to have a beneficial effect, and that they don't take a second dose at 2:00 or 3:00 a.m. where they will have clear somnolence in the morning.

So the protocol, which I have seen only once done, is to try to find what's the lowest dosage where the patients start to take twice the dose during the night.

It's a difficult protocol, but that's the real issue because you want to have a dose which is going to give sleep sufficiently during the night, not to have the patient take a second dosage at an inappropriate time. And that happens all the time. With the current hypnotics, we see that every day. So that's the real question.

DR. FARKAS: If I can ask, maybe, a question and make a comment. I'm not entirely sure I understood what you were saying about single cases. I think we're very familiar with the problem of what to do with single cases. And it's very difficult to say -- well, we kind of have a rule of thumb that one case, you don't know, and two cases, maybe you start to know. But it's very hard to know, still, what to do with that one case.

Maybe you've already given advice. Again, I'm not quite sure if I understood. Sometimes when

there's one case, the answer is to go out and find if there's a second one. And that's an option that we have.

As far as patients taking a second dose during the night, I couldn't agree more. I guess that, again, you were talking about a study design that -- it all didn't click into place with me. But the one thought I had is that there are two different kinds of problems going on. If you dose during the middle of the night, that's one kind of problem. And if a patient has somnolence the next day from taking a dose at the beginning of the night that's too large, it's a very similar problem.

So there surely is some way to weigh these things. But I guess that there's multiple interacting factors and multiple interacting dangers when talking about a high dose once at night versus risk of re-dosing in the middle of the night.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: I'm scratching my head about

the disconnect between the objective and subjective outcome measures. You showed objectively by the polysomnogram that 10 milligrams and 20 and so forth really are not that different in terms of how quickly you fall asleep, when you wake up, and so forth.

Yet the 10- and 20-milligram group subjectively, by the sleep index score or whatever that was, didn't experience any benefit. So how can they have similar objective numbers but very dissimilar subjective experiences?

DR. FARKAS: Yes. I think one thing is, I think that it's hard to know. Study 006 was small, and I think that some of the things there -- we're worried about period effects. There were some unusual differences amongst the placebo.

I don't think we have a lot of confidence in the dose-response that we see there. And it isn't unreasonable at all to look at the data and say, we're very worried that the 10-milligram is less effective on these subjective endpoints. But I don't think that's definitive. That study isn't

definitive.

If you look at it trying to account for some of the weaknesses of this small study, the differences become much smaller. So I think that's one point.

Then the question about just how to interpret the meaningfulness of a patient saying, it took me X amount of time to fall asleep. And I think that there is value in that. But I'm not sure that it's linear at all.

You said kind of the extreme case of no benefit, no subjective benefit. But we really don't think that's what's happening. So I think that what we think is more likely, especially like on night 1, is that it's a difference of, I think I fell asleep in 10 minutes versus I think I fell asleep in 15 minutes, or whatever numbers they are. You could make the numbers 10 minutes apart, or 12 minutes, or something like that.

I think that that's not really -- it's a very contrived question, actually, when trying to understand benefit. And we use that. We tell

people to use that endpoint. And of course, we'd be interested to hear if that's the right endpoint to use.

But I think it then becomes much harder to understand what it means, that there's a few minutes' difference in this endpoint. And I think, too, the point that I made before, I think it's worth restating, that we don't dose to maximum effect. It's not reasonable, actually.

We have a history of taking doses off the market for sleep drugs because they're not safe. And I think that any number of agents, a huge number of agents, you could get more sleep with more drug. But it isn't even something that people try to do, and sometimes it's something that people try to avoid to do.

DR. ROSENBERG: Dr. Portis?

DR. PORTIS: I noticed in your conclusions that one of the things you said is that the 15 milligrams in obese women and patients taking moderate CYP3A4 inhibitors leads to average exposures similar to those from 30 milligrams.

So am I understanding that includes some antibiotics? Some SSRIs? Some antifungals? I mean, a lot of things, as you pointed out --

DR. FARKAS: Right.

DR. PORTIS: -- not in the studies, but this is the clinical population we're dealing with, especially around the SSRIs. Many people would be taking them. But I wonder, does that number -- wouldn't it also apply to others? You mentioned obese women.

DR. FARKAS: Sure. Yes, yes.

DR. PORTIS: Anybody taking this drug would also --

DR. FARKAS: Right, right. Absolutely. It really -- yes. That's true.

DR. ROSENBERG: Last question. Dr. Hoffman?

DR. HOFFMAN: This is kind of an over-the-dam question. But since the phase 2 data suggested that the 10-milligram dose may be effective, why didn't the FDA encourage the sponsor to include the 10-milligram dose in their phase 3 studies? And is it possible at this point for the FDA to negotiate

with the sponsor that they offer a 10-milligram dose?

DR. FARKAS: Yes. I think that's a great question. The answer to the first one is that there's a lot of interaction with the FDA, between FDA and sponsors, as development programs are being planned. And then as data starts to come in, there isn't that kind of interaction. Sometimes there can be. But there isn't necessarily always that kind of interaction.

I think that that kind of interaction, we really focus on -- well, we specifically identify diseases, serious and life-threatening diseases, diseases with no other treatments. ALS, for one, is one that's on my team.

So a lot of the other programs, I think, really, because of resource issues at the FDA, and perhaps because the sponsor doesn't come to us and ask, that they do what they think is best. And then we see the phase 2 -- they submit the phase 2 study results to the file, but we really just analyze it along with the phase 3 data when that

comes in.

I forgot your second question.

DR. HOFFMAN: Can we negotiate with the sponsor? Can the FDA negotiate at this point to offer a 10-milligram dose?

DR. FARKAS: Yes. That's a great question, and that's what the discussion will be about this afternoon. I think, too, I tried to say without saying that we really try to use all the data that we have, and to try to understand the dose-response. There are certain rules, decision-making rules, about p values and two studies and that kind of thing. But we're actually past that because we have a lot of data.

So then we can try to just be as scientific as we can about it and say, does the data suggest this, or do we think this would be supported, without really worrying about p minus .05.

DR. HOFFMAN: Thank you.

DR. ROSENBERG: We will now break for lunch. We will reconvene in this room in about 45 minutes, at 1:15 -- so we'll stay on time -- at which time

we'll begin the open public hearing session. The room will be secured. Please take any personal belongings you may want with you at this time.

Panel members, please remember there should be no discussion of the meeting topic during lunch amongst yourselves or with any member of audience. Thank you.

(Whereupon, at 12:32 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:17 p.m.)

Open Public Hearing

DR. ROSENBERG: I have to read this script, so bear with me.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, the product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the

beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and

any organization you are representing for the record.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families. Our nonprofit think tank does not accept funding from pharmaceutical companies, and so I have no conflicts of interest.

Our think tank focuses on scrutinizing research to determine the risks and benefits of various medical products and procedures, and our main interest is promoting evidence-based medicine.

My perspective today is as someone who is trained in epidemiology at Yale Medical School; also trained in psychology. I was on the faculty at Vassar and Yale, and a researcher at Harvard, and also a Fellow at the Center for Bioethics at the University of Pennsylvania.

Also relevant today is I am on the board of directors of two nonprofit organizations that are dedicated to helping the FDA. That's the congressionally mandated Reagan-Udall Foundation and the Alliance for a Stronger FDA. I have spoken

at dozens of these meetings, and I try to focus on the products that I think are most important and where I think the expertise that we can bring might be helpful.

So I share the frustrations that have been expressed by some of the folks on the panel today. This was a very complicated set of data. I looked at the same materials that you did, I believe, and there was a lot of data. But unfortunately, from our point of view, not enough data on what we really wanted to know more about, which were the low dosage, the 10-milligram dosage. And so I want to just say a couple of things.

Our effort is always to look at the risk/benefit ratio, and I'm sure that's something that you will also be doing, and certainly that's with the FDA wants to do. What are the risks of this product, and what are the benefits, and what do we know? Do we know enough about those risks, and do we know enough about those benefits? And I felt that the FDA presentation seemed a little apologetic.

I think their determination to tease out as much information as possible is extremely important, and I think that their focus -- not just looking at how many minutes faster do you fall asleep, but to really look at what are the benefits.

When people have insomnia, it's horrible to lie in bed not being able to sleep. I'm sure everyone in this room has had that experience, and I've had it too often. But what really matters is how you feel the next day.

I am sure I'm not the only person who ever took a sleeping pill because I had a big drive the next day and I wanted to be sure that I got enough sleep. So if in fact the pill makes me sleepier or less able to drive well the next day, that's really crucially important.

I do want to point out that on page 27 of the clinical review, there was some -- it's a very clear presentation of what the benefits are in terms of additional sleep time, falling asleep faster, and staying asleep. And those benefits are

statistically significant, but they're often quite modest, especially at these lower dosages where you might have people, on average, falling asleep 5 minutes sooner or staying asleep 20 minutes longer. And that's a pretty modest benefit if in fact they're going to also feel tired the next day and more likely to fall asleep while driving.

So in summary, I would say that despite all the data, a tremendous amount of data, as the data came in and as it became increasingly clear that there were serious and substantial risks at the higher dosages, that has left us with a situation where we need better data at the lowest dosage -- that's 10 milligrams -- and we don't have that. Having 60 people in a study is just not sufficient.

As frustrating as it was to look at individual patients, and I share the concern that individual patients can tell us just so much, we're stuck with that kind of information. And it becomes important when you only have such a small number of people taking these low dosages.

So the choice is to either ask for more data before approval is given, and that is what we believe needs to be done; the other choice would be to provide really explicit labeling. But all of you in this room, I think, know the limits of labeling. Labeling is not enough. You could have a great warning. You could even have a black box warning saying, don't take this drug if you're planning to drive within 12 hours or 10 hours or whatever number of hours you might be able to come up with. But people are just not going to read it or they're not going to understand how important it is.

So labeling is important, but not sufficient to protect people from adverse reactions. And postmarket studies aren't, either. These products -- and I don't want to pick on this one pill because we know that there are problems with Ambien and other pills as well -- hadn't been studied adequately originally, and those drugs are being reviewed now by the FDA. And I congratulate the FDA for doing that.

We need to get a better sense of what the real benefits are, not just 5 minutes or 20 minutes of uninterrupted sleep, more uninterrupted sleep, but the actual functioning of a person on the next day. And we should know that information prior to approving a drug that's clearly going to be used by many, many people.

In conclusion, I just want to say that I don't envy your work today. It's very difficult to plow through all this information. But I hope that you'll be able to focus on the key issues here, which is how do we measure benefit? What is the purpose of sleeping pills? Why do people take them? Is it just that they want to fall asleep 5 minutes faster and don't want to get up quite as often during the night, or is it a bigger issue than that?

Is the real benefit how well they can function the next day, how well they can think, how well they can drive, and how well they can do all the things that we all try to do in our day-to-day life; and whether we need more data -- and I

believe that we do -- more data to find out is 10 milligrams safe and is it effective?

A related issue is whether, if the dosage is high enough to be effective, is that inevitably going to cause problems with safety? In other words, if it works to help you fall asleep, is it more likely to keep you tired the next day, more likely to have you falling asleep while driving?

Thank you very much for the opportunity to speak today, and I'd be glad to answer any questions.

DR. ROSENBERG: Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. ALMASHAT: Sure. My name is Sammy Almashat. I'm a physician with Public Citizens Health Research Group, and I have no financial conflicts of interest.

The take-away from this morning, to me, at least, is that the safety data that we have so far, especially for lower doses, is very limited. The

other outstanding question is, how will this drug behave in the real world? Especially considering that this is a first-in-class medication, it is especially important to look at the historical experience with similar drugs.

Zolpidem is one of the most widely-used sleeping medications on the market, and what did we know about this drug at the time of approval? And this is hindsight, so with all the limitations that come with that.

In 1992, the FDA concluded that pre-approval studies were consistent with the conclusion that zolpidem is not associated with residual effects the next day, and with one exception there was no evidence for next-day decrements in psychomotor function. And what do we now know?

Two large studies in Norway and France concluded that there was a more than doubling of risk of car accidents with zolpidem or zopiclone. And more recently, SAMHSA released a report showing a sharp rise in emergency department visits involving the sleep medication zolpidem; half of

those visits involved drug interactions. There's much uncertainty involving drug interactions with the current drug.

Just last week the FDA warned against driving or engaging in other activities that require complete mental alertness the day after taking Ambien CR because zolpidem levels can remain high enough the next day to impair these activities.

Here we note Ambien CR's half-life, 2.6 hours, compared with suvorexant, it's almost six times as long. In fact, suvorexant, if approved, will have a half-life longer than any other currently marketed insomnia drug, with one exception, quazepam, a much older medication that's not used as frequently.

Keeping in mind that this is meant to be a daily use drug, this will reach steady state in approximately 2 to 3 days. What does that mean? That means if patients are planning a drive, they must discontinue the drug 2 to 3 days in advance before they undertake that drive. How likely is

that to happen?

Like other sleep medicines on the market, suvorexant's marginal benefits on sleep latency and maintenance are in too many cases achieved at the expense of prolonged sleepiness in addition to suicidal ideation, hallucinations, elevated cholesterol, and possibly cataplexy and sleepwalking. Also, like its predecessors, long-term dependence ensures chronic effects. As Dr. Farkas pointed out, even though suvorexant increases sleep time, it makes many patients more sleepy, some much sleepier.

While measures of suvorexant's effectiveness are restricted to only the first 6 to 9 hours after ingestion, the drug remains effective beyond this arbitrary time frame, with dangerous consequences. And again, the terminal half-life is noted here, in addition to the fact that obese women clear the drug two to three times slower than normal-BMI men.

Low dose suvorexant more than doubled and high dose more than tripled rates of somnolence in the first 3 months of treatment. High dose

suvorexant also led to more intense and longer episodes of somnolence, and more patients on high dose discontinued due to the symptoms. And females, again, were especially affected.

Excessive daytime sleepiness is an uncharacteristic chronic and persistent sleepiness during the day. The distinction here is persistent, and also the fact that it can begin suddenly, without warning. High dose suvorexant patients experienced this about five times as much as placebo patients, and low dose patients also experienced it about twice as often.

In addition, high dose patients, 6 of the 12 high dose patients, had an onset of this reaction 3 months after starting the drug, which would make it much less likely that patients will readily tie this side effect to the drug. And as Dr. Illoh, the clinical reviewer, noted, "EDS has safety implications, especially when individuals taking the high dose have to go about their usual duties, such as driving."

It's important to remember the definitions

of somnolence in EDS in the study depended on an awareness of the symptoms. But many with significantly impaired alertness may not be aware of their state, and will therefore continue with daily tasks as before, including driving.

Two trials were conducted to evaluate the residual effect of a nighttime dose of suvorexant on next-day driving ability. These were hour-long tests conducted the morning after the dose, with lane deviation the primary outcome.

Symmetry analysis suggested excessive lane deviation with both high and low dose suvorexant, and five of only 104, 5 percent of high and low dose suvorexant patients, compared with none in the placebo or the active comparator zopiclone group, which has been associated with driving impairment, had to stop the test prematurely due to somnolence.

But the key observation here is that these studies measured driving performance in supervised one-hour increments when the patient had been explicitly warned of potential impairment. How will a somnolent patient drive in the real world

when they're alone at the wheel on longer drives?

In addition, the risks of falling asleep at the wheel, much more dangerous than slight lane deviation, could not be measured in these studies. Indeed, subjects could, and five on high and low dose did, simply stop the test at the first sign of sleepiness.

Dr. Farkas pointed out four narratives from patients on high dose suvorexant reporting difficulty driving due to somnolence. But again, this was not restricted to high dose patients, and one low dose patient fell asleep and drove across the middle line with her eyes closed.

Dr. Illoh concluded correctly that the overall assessment suggests that suvorexant-treated individuals need to avoid driving, operating machinery, or engaging in activities that require full mental alertness until they become fully awake. But how will a patient know when they are fully awake enough to drive? And how many will read the drug label at any time, but especially before getting in the car the next morning?

Even if they had insight into their impaired mental state, dependence may prevent patients from discontinuing the drug. After discontinuing high dose suvorexant and transitioning to placebo, 48.5 percent of patients achieved less total sleep than before starting the drug, a significantly higher rate than those continuing on placebo.

Dr. Illoh pointed out that while the sponsor suggests that rebound effects observed for some sleep maintenance measures do not appear to be consistent with clinically meaningful rebound insomnia, the FDA believes that sTST findings for suvorexant at both doses and in the elderly subgroup are suggestive of a rebound effect.

In addition, suvorexant seems to cause suicidal ideation. Five in the high dose group versus one in the low dose and one in placebo group experienced this adverse effect. It's important to note that both subjects in the low dose and placebo groups had a prior history of suicidal ideation. All but one in the high dose group had no such history.

There was a dose-dependent increase in total cholesterol, which Dr. Illoh concluded may not be trivial, especially if maintained over a longer period. Most patients, I assume, will take this drug chronically and daily.

Finally, you will be asked today whether a lower dose should be approved as a safer alternative to the high dose. Dr. Farkas pointed out that there is five to six times less safety data for the lower doses when compared with the higher doses, and these were the 15- and 20-milligram doses, not the hypothetical 10-milligram dose.

Especially when considering that the true low dose for female and obese patients is unknown and may be much lower than 15 milligrams, this represents a dangerous lack of safety data for lower doses. But even with the limited data available, the rates of somnolence were doubled in low dose subjects, and driving was significantly impaired on low doses of suvorexant.

Dr. Katz concluded that if a dosage strength

lower than 15 milligrams is unavailable, we would need to consider if the drug could be marketed safely at all, something that was discussed this morning, if we believe that a substantial proportion of the indicated population needs a lower dose. And up to one-third of the targeted population may be female, obese patients.

In conclusion, given the plethora of risks both to patients and the public, suvorexant should not be approved. The risks are evident at the lowest dose up for approval, and amplified in women and obese patients. And again, the half-life of this drug would be longer than any other drug on the market with one exception, a much older benzodiazepine that's rarely used.

Labeling cannot protect patients from risks of which they are not aware, such as unconscious mental impairment. And here the risk of driving is particularly important, even if it is within the label, even if the patients do read the label. If this is a daily medication, how often are patients not going to drive the next day; in other words,

every day?

That is crucially important, especially for this drug, which takes 3 days to be fully eliminated from the body. This requires advanced planning, 3 days in advance, before a long drive. The dependence potential ensures that many patients will choose to live with side effects than suffer rebound sleep disruption.

Therefore, it is critically important that the committee consider these findings, and the fact that while a hypothetical 10-milligram dose could be safer and effective, it is not currently being offered today. Therefore, the drug cannot be approved based on the data we currently have available. Thank you.

DR. ROSENBERG: Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ROSENBERG: Good afternoon, everyone. I'm Dr. Russell Rosenberg. I'm the chairman of the National Sleep Foundation, and on behalf of the

National Sleep Foundation, I'm really grateful for the opportunity today to speak about how important the role that effective pharmacological interventions have on improving the health, public safety, and overall quality of life of millions of Americans suffering from insomnia and other sleep disorders.

While I'm here today as a representative of the National Sleep Foundation, I would like to disclose that in my work as a sleep specialist and researcher in Atlanta, I have received research funding from Merck.

The National Sleep Foundation is an independent 501(c)(3) scientific and educational foundation that is supported by contributions from individual and member contributors, as well as unrestricted educational grants from government, foundations, and corporations.

The National Sleep Foundation has received educational grants from pharmaceutical companies such as Merck and Company. In 2012, however, the National Sleep Foundation educational grants from

pharmaceutical companies represented less than 5 percent of NSF revenues.

The NSF is a national nonprofit organization dedicated to improving sleep health and safety through education, public awareness, and advocacy. Since our founding over 20 years ago, our organization has been the leading organization representing and advocating improved sleep health and safety for the general public.

While sleep is a vital component of our health and it has tremendous impact on our daily lives -- I think everyone here would admit to that or agree to that -- how well we think and work and interact with others is also affected by how much we sleep. But for some, getting the sleep we need to function to the best of our abilities and feel well isn't that easy. Some individuals have trouble falling asleep, some have difficulty staying asleep, or some even experience unrefreshing sleep, sometimes even all three. Sometimes these problems are acute and other than times more long-term.

Insomnia, which is the most common sleep complaint amongst adults, is much more common than sleep apnea and some of the other sleep disorders. The National Sleep Foundation's annual Sleep in America poll routinely finds that more than half of respondents report having at least one night or more, even sometimes a few nights a week, having symptoms of insomnia.

Insomnia impacts millions of Americans and their families and social networks as well as the public's health. It is no wonder that so many individuals are seeking information and relief from their insomnia.

We've been seeking an answer to insomnia for a long time. Some of us here today are old enough to remember back in 1977 when President Carter called for studies to review the safety, usefulness, and prescribing of sleep aids. Two years later, in 1979, the Institute of Medicine issued the landmark 198-page report titled, "Sleeping Pills, Insomnia, and Medical Practice," closely followed by the creation of Project Sleep,

the national program on insomnia and sleep disorders.

The goals of the project included looking for improved treatment options for insomnia, better prescribing practices, and education for healthcare professionals, and support for research about insomnia and sleep aids.

Today, about 35 years later, we're brought together to consider a new treatment option. Sadly, the pace of innovation and change did not meet the ambitious goals of the seminal report and project from the '70s. Yet the need for effective and safe treatments for insomnia has continued to grow during the decades since.

The National Sleep Foundation's Sleep in America asked respondents how they use various sleep aids specifically to help them sleep. Unfortunately, many respondents were more likely to report relying on alcohol, beer, and wine than in OTC or sleep medications prescribed by a doctor.

We obviously need a better solution. Patients should be empowered to ask for and receive

help for their insomnia from their healthcare provider. Every patient visit provides the opportunity to assess someone's sleep, a vital sign of health. And no sleep/wake concerns should ever be dismissed.

The National Sleep Foundation recognizes there is no such thing as an ideal hypnotic, and sleeping pills are not for everyone suffering from insomnia, and that non-pharmacological interventions are effective but not widely available.

It is our position that patients and their physicians need more choices for treating insomnia. We are all aware that it has been a long time since a new mechanism of action for a pharmacological sleep aid has been approved in the U.S. Physicians and patients need more options for safe and effective treatment for a condition that affects tens of millions of Americans every night.

The National Sleep Foundation welcomes innovation, development, and introduction of more effective insomnia treatments with fewer side

effects. We encourage the scientific examination and subsequent introduction of drugs with new neuropharmacologic targets and mechanisms of action.

We want to give patients more options to obtain the treatment that works best for them. The National Sleep Foundation is encouraged that a new treatment for insomnia is being discussed today as an option that may bring relief to the millions of Americans who are waiting for better sleep.

Thank you very much.

Questions to the Committee and Discussion

DR. ROSENBERG: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We will now proceed with the questions to the committee and panel discussions, which the committee should all have in front of them. I

would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will be voting a little later. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and they will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

Next we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions

have been answered or discussed.

Efficacy: "For" -- I'm going to mispronounce this. Suvorexant, is that right -- "suvorexant, the applicant seeks an indication for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance. The proposed dosing algorithm includes higher and lower doses for non-elderly and elderly patient populations."

Just to summarize, for non-elderly, starting dose 20, high dose 40 milligrams; for elderly, starting dose 15 milligrams and high dose 30 milligrams.

First question: "Please discuss whether separate doses are necessary for non-elderly and elderly patient populations."

I turn the question to the committee. Dr. Clancy?

DR. CLANCY: I was interested to hear that internists taking care of patients over 65 note that a typical patient may be co-consuming five or more other medications, and that we have limited

information regarding induction of metabolism or inhibition of metabolism.

So insofar that this population may have more complex biochemistry than someone who's drug-naive or on one medication, I think it might be prudent to have separate doses for the elderly versus non-elderly, perhaps more as a surrogate for their medication complexity rather than any specific population differences in PK.

DR. ROSENBERG: Dr. Rizzo?

DR. RIZZO: I think it's reasonable to consider the separate doses for the elderly and non-elderly. What I feel slightly uncomfortable about is age itself being a surrogate for other things that are going on that we don't know about from the data that has been presented. And I think it would be better to know what those issues are, whether they're medical impairments or lifestyle issues, other demographic factors, that can help guide a more focused recommendation rather than just elderly versus non-elderly.

DR. ROSENBERG: I'm an Alzheimer's

specialist, so I spend all my life treating frail, elderly patients. I think that if the FDA moves toward the 10-milligram dose, that the most prudent thing is to simply say everyone starts at a low dose. I realize that's a later question, but these two are integrated here. What's the important point is I think it's not just elderly. It could be obese. It could be women. It could be people taking other medicines.

So in a sense, I think the safest approach would be let's pick the lowest dose, advise everyone to start with the lowest dose, and then have cautions about certain groups you should be more cautious in increasing the dose. I think elderly is just one of them.

Dr. Zivin?

DR. ZIVIN: I think it's clear that new options are necessary for treatment of insomnia. Benzodiazepines have been highly effective in the past, but something new may be helpful to people who are not currently well-served by the currently available options.

All patients need to have their doses titrated, and this drug will be no different in that regard. And of course, we always start out with the smallest dose and then work our way to the place where the people need help.

It appears that the drug is reasonably safe, or at least as safe as other drugs in the same category. So I only have one question left of the sponsor, and that is, what do you expect to be the trade name of the drug?

DR. MICHELSON: I'm afraid we don't have an answer for that.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: I want to go back to that distinction of non-elderly/elderly. Our largest problem in sleep medicine is to deal with Alzheimer's patients, and we have more and more Alzheimer's. And we see an aging population; we will have more and more.

The number one problem in Alzheimer's, the safety problem, is that they don't sleep at night. They don't recall. They burn their house. They

burn themselves. They injure themselves. And we have no way -- there is no current drug which can help the sleep of the Alzheimer patient, the demented patient, and a certain number of neurology core patients, the Parkinson's patient, the REM behavior disorder patient.

So I believe that the issue is not non-elderly/elderly. It's subjects who have an impairment, an impairment at night, and we never consider these things. We approach the wrong way.

I heard what was told about we have to be safe. We have to be safe every day. I hope that Dr. Chervin will report on his study in the elderly in the community and how to treat insomnia or not to treat insomnia and what are the consequences. But one thing that we have to realize today, we have a larger and larger population that we don't deal with, that we leave at risk, at risk of killing others, just because we don't treat them.

I'm saying that we have to really make a big effort to find new molecules that are more efficacious than increasing total sleep time by 10

to 15 minutes per night, which is what zolpidem, zopiclone, and all the Z drugs do.

They are different chemicals, and we cannot make the chemicals. We have to look on where do they act, and I don't think that we should go to non-elderly/elderly, but look at what are the impairments that the subject has and what really we want to treat.

DR. ROSENBERG: Dr. Kramer?

DR. KRAMER: Yes. Thank you. We heard what FDA has concluded from its evaluation of the response concentration information, but we really didn't have a chance to hear from the sponsor, who really focused on the pivotal trials. It would be interesting, I think, to hear their explanation of these lower doses, et cetera.

DR. ROSENBERG: We'd be happy to hear briefly from the sponsor about the question of a 10-milligram dose.

DR. STONE: Hello. I'm Julie Stone from modeling and simulation, and I'd like to tell you about the exposure-response work we've done. We

believe that these analyses support two conclusions that differ from the FDA's.

One, we believe that both efficacy and safety are dose-related over the clinical range we're discussing. And two, we don't believe that 10 milligrams would be an effective dose. What I'd like to do is take a few minutes and walk you through the data that support these two conclusions.

If I could have slide 1429. Slide up. This speaks to the analyses that were done. In looking at exposure-response, what we want to do is look at the totality of the data. Could we have that slide up? So we wanted to ask a question about, what do we know about exposure-response, given the totality of the data?

So what we did was we pooled the large data set that we could obtain from phase 2 and 3, including the long-term safety study, for safety analyses. And we pooled across time points, looking at zero to 3 months. So looking at this large data set, we examined this effect.

I do want to point out one difference with the FDA analysis. In the studies in phase 2 and 3, we sampled, for PK samples, only the morning after the patients were bedtime-dosed. So all our concentration measures are really around 9 hours post-dose.

We made no effort to extrapolate to an AUC value from these, which presumably -- I couldn't tell in the FDA background, but presumably that was what must have happened -- because we really think that that C-9hour better reflects the limitations of that data set we have for exposures in these patients.

Now, in the systemic approach that we took to the modeling analyses, we looked at statistical approaches to really answer the three questions at the bottom of this slide. The first question we wanted to ask was, recognizing the limitations of C-9hour, would C-9hour or dose be a better predictor of response?

Then the second important question I think everyone's been discussing is whether there's

evidence of exposure-response in the data. And lastly, we did some work to identify covariate.

If I could have the next slide. So what I want to do in the next few slides is really work through what we found in the answers to those first two questions. In the first question, really, about C-9hour versus dose as a predictor of response, what we actually found depended on what we were looking at.

For the residual effects, we found C-9hour was the best predictor. And this made sense. This is the concentration in the morning when most of the patients are experiencing these effects. But what we found for efficacy is that dose was in general a better predictor across all the endpoints than C-9hour. And I think this really reflects the limitations in the PK sampling here in that this is morning-after concentrations, not concentrations around the time that people would experience the efficacy. And I think we also have to keep in mind these are plasma concentrations, not brain concentrations.

So when we move forward, we did residual effect modeling and we came up with very similar answers to the FDA in terms of C-9hour effects. But where we differ is in what we found in terms of the efficacy. And I want to focus on that in the next slide, if we can go to that.

What you've seen in some of the FDA's presentation are an approach that we also took. We looked at some exploratory plots of exposures and dose versus response. But then we also stepped back and we did a statistical test using two models that are actually very similar, but we force in one model for dose-response to be flat, and in the other we allow it to vary by pharmacological manner, like an Emax. We can ask the question of whether there's significant evidence for a dose-response in these efficacy measures.

The table on this slide shows the results in the central column here. For all endpoints except LPS, we found significant evidence of a dose-response in the efficacy. And what you see in the final column to the right are the estimated effect

doses for 50 percent of maximum response. These generally fall in the 10- to 20-milligram range.

So what I'd like to do as we move to the next slide is really then take these models and say, using those in a simulation mode, what do we understand about dose-response? And this slide is a bit busy, but -- can we have the slide up? Thank you. It's a little busy, but it really does try to summarize what we understand about the balance between efficacy and safety in terms of dose-response.

What you see to the left are four panels that depict the mean placebo-corrected change from baseline for four key efficacy endpoints in the solid lines, with the dashed lines showing the 90 percent confidence intervals. The color code is, the yellow is the non-elderly, the orange the elderly. What you can see for the all the measures except LPS is that we really do predict and show a significant dose-response relationship across the dose range that we've been discussing today.

Similarly, for the residual effect measures

shown over on the right, the probability of occurrence of a residual effect of any duration or intensity would increase with exposure, with dose. So we agree with the agency.

But we believe together that this analysis supports, as we're talking about dose options for suvorexant, that there is a tradeoff between efficacy and residual effects across this entire dose range.

What I'd like to do is actually wrap up this discussion talking a little bit specifically about the 10-milligram response and what do we project the 10-milligram response to be.

I'd actually like to start that discussion by sharing some of those exploratory plots that you can generate for the subjective measures. In the FDA's presentation you saw some exploratory plots for the objective measures. I'd like to show you some of the subjective. Could I have slide 1466? Yes. Slide up.

So what's depicted in this plot -- this is a plot of the -- this is not a model. This is

observed data for the subjective sleep onset measure. What's plotted in the top row are the responses versus the dose in this pooled data set from the three trials at three different time points, week 1, week 4, and week 12.

In the bottom we plot that same data, but now looking at it from a concentration standpoint. So the leftmost point is the placebo response, and then the responses in all the active suvorexant treatments are divided into quartiles based on their C-9hour value.

Now, I'd said that dose was a better predictor of response for these efficacy measures, but we do see this relationship as well with concentration. And what you see is a very convincing relationship where the response is very dose- or concentration-dependent.

If I could point out the points that are closest to the placebo response that might reflect a 10-milligram response, what you see is these are really quite small and not very different from the placebo response.

Could I wrap up with slide 1433? If I show total sleep time, that would also, that subjective measure, have a similar relationship.

So to sum up what we know about the 10-milligram, or what we would project based on the modeling for the 10-milligram response, that's depicted here. And this is a slide very similar to the one that I already showed depicting the dose-response.

But what we superimposed on here with the vertical lines are the location of the 10-milligram. And the numerical values shown on this figure are the mean predictions that we have for the 10-milligram response based on the totality of the data that we've collected in phase 2 and 3.

As you can see, in most of these measures, we really predict that we're pretty well down on the dose-response curve. And I would particularly draw your attention to the bottom row of the efficacy measures, where we're projecting mean responses of like 2 minutes or 4 minutes improvement, or maybe 10 minutes until sleep time.

We do not believe that these would be clinically meaningful or perceptible to the patients.

I would also point out, if you look at the somnolence on the upper right, that we would still predict that the patients would have an elevated somnolence rate. Even at this 10-milligram dose where they're not getting effective subjective treatment, they would have a rate predicted to be 5.9 percent relative to a 3 percent placebo rate.

So we don't believe you can dose down and avoid the residual without giving up the efficacy that is needed for this treatment.

DR. ROSENBERG: Thank you.

Dr. Portis?

DR. PORTIS: Well, I want to echo some of the things that we said. I'm a little uncomfortable with the question about the elderly because I think there are safety concerns that we're seeing in this at any age. Certainly people are living longer and are active longer, and 65 is considered elderly but it's not old. And people are still very active at that age and driving. And

we don't have complete data, safety or otherwise, on the lower dosage.

As I said, I think that we have real concerns about safety already with the information we know. And as was pointed out, we can't assume that if we go to a lower dosage, that people won't be double-dosing themselves and taking more, which just gets back to the problems we're trying to get away from.

The other thing that we haven't discussed, and it applies to everyone but particularly the elderly, is around the lab results, things like higher cholesterol and how that may be even more of a problem if we're just talking about dosage for the elderly. So those are my concerns.

DR. ROSENBERG: One more comment. Dr. Chervin?

DR. CHERVIN: Just directly on this issue that we're asked to discuss at the moment, whether separate doses are necessary for non-elderly and elderly, and when you say separate doses, I assume that we're talking about the ones that are proposed

here and that were tested.

To me, it's important that the data that we really have are really very little on any doses except 30 milligrams and 15 milligrams in the elderly, and 40 milligrams and 20 milligrams in the non-elderly.

So because those are the sets of data that we have, I think it's hard to speculate about whether it was necessary to plan the phase 3 trials that way. So given the data that we have, it's a question of, with these data, do we have efficacy and do we have safety?

So in my opinion, I'm so far leaning that we do have efficacy and we do have safety. And I think that the data, as shown, are probably the data that I would think would be appropriate to use if this drug were going to be used at this point.

DR. ROSENBERG: Let me conclude -- oh, Dr. Katz?

DR. KATZ: I just had a question. We saw a lot about the 10-milligram dose and what we know about the 10-milligram dose. We saw a lot of

sophisticated modeling just now about dose-response and that sort of thing.

But let me just ask you, there was a trial that looked at 10 milligrams versus placebo with this study 6, and other doses, obviously. My understanding is that, analyzed according to protocol, the 10-milligram dose was statistically significantly better than placebo on sleep efficiency, which is not the traditional outcome but it was the primary outcome. And it was also clearly statistically significantly superior to placebo on objective WASO.

Am I right about that? There might have been a dose-response, but I'm just trying to get back to some sort of simple, straightforward analyses of the 10-milligram dose. And at least two out of the three primary outcomes, if we want to call them, or important outcomes in that study, the 10-milligram dose was clearly separated from placebo. I'm not talking about dose-response now. I'm just talking about whether or not the 10-milligram dose showed efficacy.

DR. HERRING: In response to your question -- we can put slide up. This is from the core presentation, where we showed the efficacy from the phase 2b study, and as you mentioned, showing that sleep efficiency was significant at night 1 and at the end of week 4, as were the other doses. And on night 1, there's evidence of a dose-response in both cases.

As I pointed out in the earlier presentation, 10 milligrams was the least efficacious of those doses by this measure. The next slide shows the two objective measures that are more typical, as you know, for approvals, and required for approval of sleep medications, which are the LPS and the WASO measures, where we've talked about LPS and the period effect due to carryover, and the fact that we're looking at period 1 data here. And this shows more or less no dose-response for that measure, whereas for WASO, and particularly on night 1, we do see a dose-response, where 10 is the least effective and 40 and 80 maximally effective. But again, as you

point out, there is an effect here for WASO. So we have sleep efficacy and WASO effects that were measured objectively.

Then the next slide, as you know, is where we went in and looked at the subjective data -- if we can move to 24 -- for the onset measures and the two maintenance measures. We see that neither 10 or 20 are effective by this assessment, and 40 and 80 improved subjective sleep onset and sleep maintenance.

Because this is a disorder that is really characterized by patient reports -- it's actually a subjective disorder -- it's important that we be able to show effects subjectively. And this actually was really critical for us, understanding that we needed to have two replicate 3-month studies with multiple endpoints that included subjective endpoints that needed to be attained after 3 months.

I would like to show one additional piece of data. We talked about the Insomnia Severity Index and its relevance, and the fact that it's a

patient-reported outcome that reflects more of a composite picture of how patients respond to a medication.

This is showing now the ISI for the phase 2 data -- slide up -- where 10 milligrams, by this measure, was not effective. And we see nominal p values that are significant, beginning with a 20-milligram dose, and for the other doses as well.

So I wanted to also point out that on another subjective measure, the ISI, we also see a dose-response, indicating that 10 milligrams is ineffective from a patient perspective.

So we have this, as you asked the question about what we have in terms of actual data from the trial versus model data, as Dr. Stone pointed out. And what we see in the overall picture is that 10 milligrams is not an effective dose.

DR. ROSENBERG: We've had a lot of interesting discussion, and some of it relating to later questions. Oh, Dr. Unger?

DR. UNGER: Yes. I have a comment. Maybe we're getting carried away with individualized

medicine at FDA. But in the last few years, we've been paying more and more attention to cumulative distributions. We recognize that if we look at mean effects, that there in fact are some individuals who will respond.

I think that's kind of the theme here, is that if there are some individuals who would respond to 10, then why not give them 10? And so I think that along with the safety data, where you show no mean effect on some safety parameter, we're interested in the outliers. And it's similar for efficacy.

So if there are some patients who would respond, that could be a good thing. I just would throw that out there.

DR. ROSENBERG: So I'd like to summarize the discussion on question a: Please discuss whether separate doses are necessary for non-elderly and elderly patient populations.

I think I can summarize the conclusion as being inconclusive. I do not think the committee has agreed on any consensus that we should have the

separate doses. I've heard a more general concern about dosing in many populations, but not specifically to elderly.

I think we need to get back to the 10-milligram question after we encounter the other questions. It's a crucial one, but it's just not for here.

Here's a big question: Please discuss separately the evidence of effectiveness in improving sleep onset and sleep maintenance."

Dr. Chervin?

DR. CHERVIN: I wanted to preface by a comment. A lot of people have talked about subjective versus objective today. And so after a little more than two decades seeing sleep patients, I wanted to comment on that.

It's very true that insomnia patients care about their subjective symptoms. It's all about that. We know from many decades of trials with hypnotics that hypnotics do not change the objective measures on polysomnography, which I do all the time. We do it all the time. It's our

gold standard measure for physiological sleep. Hypnotics don't change those numbers very much.

They can have a large impact on a subjective experience and a small impact on the objective numbers. So I personally think that the subjective numbers, if anything, are more important than the objective numbers. And, by the way, the reason is because insomnia is largely a perceptual phenomenon, and we haven't figured out the physiology of what leads to that perception.

But to me, that's the important thing. And in my view, from the 429 pages and what we have heard today, I would think that this medication looks effective -- certainly for sleep maintenance, but I also say perhaps not quite as robustly, but also for sleep onset in both objective and, more importantly, subjective measures.

DR. ROSENBERG: Dr. Cohen?

DR. COHEN: This is a question, Dr. Chervin. Explain to me, as someone that's been seeing patients a long time but obviously not a sleep medicine specialist, why with treatment do people

have more somnolence and excessive daytime sleepiness on medication versus placebo, and then that makes their quality of life or experience or whatever, insomnia, better?

DR. CHERVIN: Most of the patients that I see, when we get rid of their insomnia, they feel better. So I'm not sure we can extrapolate from the evidence we saw today about what happens in general with insomnia patients.

Insomnia patients feel fatigue, tired, malaise during the day. They don't necessarily fall asleep, and so some of them don't say that they're sleepy during the day. In fact, if you did an MSLT, which is a gold standard measure of objective sleepiness during the day, on an insomniac patient, you wouldn't measure that they're able to fall asleep very much.

So I think there are a bunch of different issues at play. But also relating to your question and what somebody else asked today, I don't think that what an insomniac is mainly necessarily interested in is their daytime function.

The experience of having a bad night's sleep is bad, and they don't like it, and they want to get rid of it. I think if you can help their daytime function, too, that's great. But I think what happens at night is an important issue.

DR. ROSENBERG: Dr. Bagiella?

DR. BAGIELLA: The result that we have seen in the reduction of the time awake, I think it is, or the increased time which adds up to minutes, not hours, is that something that is comparable to other drugs that are on the market and is something that is clinically significant, clinically relevant? Because it seems like gaining 20 minutes a night or 40 minutes a night in a long, 8-hour night is not that much in the end.

DR. CHERVIN: If I can help address that, although there may be others in the room also. From the trials that I've seen in the past, you don't achieve more than this range of a 10-, 20-, maybe 30-minute change in objective sleep at night. That's all the hypnotics we have. My impression is that that's what they've been shown to do.

Fortunately, the symptomatic improvement that goes and correlates with those small objective changes are greater.

DR. ROSENBERG: Do you think that effect size is clinically important, clinically relevant? Do you think that's enough to help people?

DR. CHERVIN: Well, yes, I do. I'm not sure that it's those small minutes that is the main help. I personally think that it may be the influence on their subjective overall experience that has more to do with it.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: Yes. We have to also realize the limit of our objective test. You know, we score sleep grossly. What we call an arousal, it's 3 seconds. Your brain doesn't react in 3 seconds. It's in milliseconds. Clearly, when you look at the EEG of a sleep patient, you can see that their brain waves operate differently there. When you use a computer, you can show more differences than looking visually.

So our measure is the limit of what we can

see and not really probably demonstrating how much the brain changes with all these drugs. We have to find better technique that we do not have right now.

DR. ROSENBERG: I have to say I'm not a sleep specialist, just a person who does a lot of trials in other diseases. And to me, the overall pattern of efficacy is very persuasive. The effect size, I'm relying on sleep specialists to say that's enough. It seems plausible that's enough. But what I see is a pattern that's just very consistent.

Yes, it's a little more consistent for the high dose than the low dose, but there's nothing going the wrong way. There's nothing really kicking out at you. And chances are that the -- what is it -- the one finding that was not significant in 029 might be attributable to random chance; even after correction for multiplicity, you still have 20 comparisons, or you can easily have one that's not. So I'm really persuaded of efficacy at these doses.

Dr. Schwartz?

DR. SCHWARTZ: I was just wondering -- I mean, I think there is a difference, though, in efficacy between sleep onset and sleep maintenance, since that was the question. It seems like the results are more robust and the magnitude of the effect is stronger for sleep maintenance than it is for sleep onset.

DR. ROSENBERG: Dr. Morrow?

DR. MORROW: Yes. Just a follow-up on the objective versus subjective measure issue. I'm not an expert in these areas, and I take the point that sleep complaints are a subjective experience. And that's important. I'm not sure about the psychometric properties of these particular subjective measures. How reliable are they?

DR. CHERVIN: The kinds of measures that they have used in the study are the typical ones that have always been used. So these are typical ones, to ask the patient what their perceived sleep latency was or ask them how much time they felt they were asleep, or subjectively ask them about

the amount. The ISI was also -- we saw data on the Insomnia Severity Index. It is very widely used.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: I would like to add, we talk about data and consequences. What we forget are all these very large studies, which show that insomniacs have much more absenteeism. Their blood pressure increases. Their falls increase if they are elderly. They have more cancer now. They have a lot of other issues which are very well demonstrated by general population studies.

So it's not only daytime somnolence or what they feel during the daytime. It's that insomnia has an overall heavy cost, and in general internal medicine. And if you don't treat chronic insomnia, you decrease life expectancy.

So we are talking about a very generalized illness. And we are forgetting that, and we are not addressing it for sure here.

DR. ROSENBERG: Dr. Rosa?

DR. ROSA: I was just going to add a little bit on the validation issue. Normals and

insomniacs both tend to overestimate sleep onset. For example, with respect to an EEG, their estimates are longer, and insomniacs are longer than normals. So there's this consistent effect. Then if you give a medication, you might reduce both EEG sleep onset and subjective onset. But the difference remains consistent between normals and insomniacs, where insomniacs will tend to overestimate with respect to normal.

I just remind the committee, though, that EEG, like Dr. Guilleminault said, is not -- it's a gold standard, but it's not pure gold. So there's a considerable amount of error in that, and if you go look back historically, the original measuring system was validated against behavioral and subjective reports. So there's a little bit of teleology there, so just keep that in mind, the whole measurement issue.

DR. ROSENBERG: Dr. Cohen?

DR. COHEN: So I clearly understand insomnia is bad for you and it can cause a number of health problems. I understand that, taking care of

patients. But I guess my problem -- and I understand that the present medications have limitations, and all of us as clinicians want more medications for our patients so we can help them.

But what I'm having trouble with is there's all of these objective measures that don't seem that strong to me, as someone that's done drug trials and all of that, and that which Dr. Chervin, who's obviously much more expert than I, says, well, it's really the subjective that matters. This is really what you're looking at. And that's what I'm having the problem with.

Be it that I'm being dogmatic or whatever, it just seems that objective measures aren't as robust or strong. And what you're relying on, which I understand, is the patient feeling better. But I'm having trepidation about that. That's all.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: My comments are going to address the two objective measures about time to fall asleep and sleep maintenance. When I look at the data, it looks like there is pretty substantial

evidence that the drug substantially helps maintain sleep in terms of the numbers. There are substantial numbers here.

I have to wonder, however, when Dr. Farkas gave his presentation, he reminded us that if you're going to take this medication right when your head hits the pillow, you have to swallow it. It has to go in your stomach. It has to be dissolved. It has to be absorbed. It has to be circulated. And that's got to take some time. If the starting point is literally when your head hits the pillow and when do you fall asleep, that has to be confounded by all the issues of drug absorption, distribution, metabolism, and so forth.

I have to wonder, why wouldn't you instruct a patient to take it 30 minutes before you go to sleep? Because if the maximum blood level is around 2 hours or so, that may explain why there's a better maintenance effect. There's more in your system to get the job done. But there must be a minimal amount when you're first trying to fall asleep. And that's why earlier I had asked for a

picture of the PK to see how much is actually showing up in those first 20 minutes. It must be very low.

So I just don't understand the rationale for not saying, take it 30 minutes before you want to go to bed, and there'll be enough in your system that you'd have more observable effects.

DR. ROSENBERG: Dr. Dimova?

DR. DIMOVA: Actually, I can try to address the first question, how long it takes. Usually after the first dose, the first may be half an hour, almost -- there is almost no plasma; I mean effective plasma levels, in most patients. The first half-hour, first 30 minutes, there is almost nothing the first night. Yes.

As Dr. Farkas showed on the graph, actually, what happens is that's why there is a little bit better efficacy week 1 versus day 1 for the low dose, because actually there is accumulation. So the second, third day, you usually start with some residual levels. And then after you take the drug, there is also -- it takes about maybe 15, 20

minutes again for the drug to reach a certain plasma level.

Actually, there is a threshold which the sponsor started the development program, .4 micromolar. And I know that just based on the phase 1 trials in which we have done sampling, it's pretty much right on the target.

Actually, they did a couple of phase 1 studies in which again it was subjective, but they had like lights off at 30 minutes and 2 hours. At 30 minutes almost nobody, actually 0 percent of the patients, reported somnolence versus almost 100 percent of patients reporting somnolence after 1 hour.

So for me, I think you are making a very good point that this drug is ideal for being recommended to be taken at least half an hour before going to bed.

DR. ROSENBERG: Dr. Voas?

DR. VOAS: I would like to just raise a couple of points in urging caution here. We've tended, I think, in this session to set aside

alcohol because it's not exponentially impacted, the two of them together, but only additive. But keep in mind that our criteria here was .05. You add alcohol to that, you're now getting into the level of .08, which is illegal.

We've been studying the early morning presence of alcohol in individuals that drink heavily the night before, and we find that that is predictive of recidivism for drinking and driving, and that there is a significant carryover from heavy drinking in many individuals.

This is of course speculation, but if you consider someone who drinks heavily at night and then takes a sleep aid such as the one we're discussing, then in the morning, they're likely to have the combination of the two.

Because of the stimulus effect of alcohol as well as its sedative effect, it's likely that at nighttime they're going to have a hard time getting to sleep, so they may overdose. And so then in the morning, you have a particularly dangerous situation.

Now, that's speculation. I don't have the data on that. But I just urge caution in thinking about the effect of carrying over sleepiness from these drugs into the morning because it is a complex driving situation.

DR. ROSENBERG: I just want the committee to keep in mind, we're still talking about efficacy. Questions 4 and 5 are going to be adverse events, so Dr. Voas's comments are totally apt to questions 4 and 5.

Dr. Guilleminault?

DR. GUILLEMINAULT: You know, when you talk about PK, the first thing that if you ask yourself, do I know exactly when I fell asleep last night, none of you will be able to do it because we have an amnesia, which is just before you fall asleep, which is about 10 minutes.

If you look at the objective measurement, it takes about 20 minutes for anybody normal to fall asleep when they turn off the light. You don't believe it because you don't have your memory to tell you that, but that's the objective data.

When you take a pill, you don't take it when you put your head on the pillow. You go, you have a glass, you drink it with water, et cetera. So most people usually take their pills about 15 minutes before they go to bed, take 20 minutes when they turn the light off. So you have some delay that you can use to see absorption.

I agree that it will be very important to indicate when you need to take the pill before you go to bed based on the pharmacological data. But we have to remember the reality of what sleep is, also.

DR. ROSENBERG: Since we're talking about efficacy, we've heard a number of opinions about the drug. I want to hear, does any -- I haven't heard an opinion yet that the drug lacks efficacy. And before we get near voting, I'd like to know if anyone has that opinion and hear from them.

Dr. Schwartz mentioned differential efficacy between the two indications. And one question I have to Dr. Katz is, do we have to vote on both indications together, or do we vote on them

separately?

DR. KATZ: Yes. I was just looking at the question. It asks both together. But we are interested in whether or not you think it works for both or whether you think it works for one symptom or another.

DR. ROSENBERG: So with your permission, can we vote on both? Or do we need to vote on the two together?

DR. KATZ: Well, we want a clear statement about what you believe. So I guess technically if you voted yes to the question, does it work for sleep maintenance and sleep onset, we could interpret that to mean that you think it works for both. But it's probably better if you split it. I think it would just be a clearer signal to us as to exactly what you meant.

DR. SCHWARTZ: And are we going to split the vote by -- oh, sorry.

DR. ROSENBERG: Dr. Mielke is next.

DR. MIELKE: Thanks. Yes, I just had a clarification. First of all, this is the 20/40 for

non-elderly, 15/30 for elderly right now. And then there's been a lot of discussion with subjective and objective, but from the FDA standpoint, it's supposed to reach both, be significant for both. Right? Or is that up for discussion?

DR. KATZ: Yes. I kind of missed the beginning of the question. But if the question is, does it have to reach statistical significance for each of those to grant each claim -- is that the question, or is that the comment?

DR. MIELKE: Yes. For both objective and subjective.

DR. KATZ: Oh, for both. Well, the protocol says you've got to win on both. If one slightly misses on one, the usual standard, you can interpret that the way you want. Strictly speaking, a given dose should win on both the subjective and the objective measure, whether it's sleep maintenance or sleep onset. But we're willing to hear what you think about that.

DR. ROSENBERG: Dr. Chervin?

DR. CHERVIN: I have another clarifying

question. It used to be that the length of intended use -- in other words, short-term for night or a few nights versus chronic use -- was a big issue. Are we considering that in this question?

DR. ROSENBERG: Dr. Katz?

DR. KATZ: Well, I think we are asking you to decide whether or not you think the study is positive. We actually don't. I don't believe any of the indications for the hypnotics say, use only for one night, or it works only for one night. There's language about, if it's not working within 7 days, think about another diagnosis.

But the indications technically I don't believe limit the duration for these drugs. So we're thinking more in terms of chronic or what happens over the course of the whole trial, not just the first night. We don't break those indications down that way.

DR. ROSENBERG: Dr. Schwartz?

DR. SCHWARTZ: I just wanted to clarify whether the vote will be about each indication

separately and the high dose versus the low dose, whether we were clumping them together if we had a different feeling about them.

DR. KATZ: Well, look. It's always more complicated than you think when you're writing these questions.

(Laughter.)

DR. KATZ: But we want to know what you believe about all of this. So do you believe that it works for sleep maintenance at the high dose? Sleep onset at the high dose? Sleep maintenance at the low dose? Sleep onset at the low dose? And then, of course, we have elderly and non-elderly.

So we want a clear view from you about what you think about all of that -- doses that are proposed to be recommended and indications that are proposed to be indicated.

So however you think you can give us that answer, if we have to change the question and break it down one by one, I guess we can do that. But that's what we want to know from you.

DR. ROSENBERG: I would like to point forth

the idea that we simply differentiate sleep onset and maintenance, and vote on the doses together rather than have four different votes. I do think sleep onset and maintenance are different indications, and they're clearly distinguished in the research.

With the committee's permission, could we divide it up into onset and maintenance?

DR. KATZ: (Nods head affirmatively.)

DR. ROSENBERG: Further discussion?

(No response.)

DR. ROSENBERG: Okay, they're going to retype the question. But while they're retyping the question, let me try to summarize the discussion.

There was a remarkable lack of controversy about efficacy. Actually, what I'm finding are -- to conclude, I think there are some points about the consistency, about the effect size, the robustness of the results.

But what I think -- let me know if I'm wrong; raise your hand about any of this -- but

nobody said the drug lacks efficacy. And then there's a question about the two indications, which was why I suggested that we split them up.

There was a further discussion, which isn't really directly related to efficacy but it's really important for the drug, of the timing because I heard no dispute to the idea that the pharmacokinetics suggested that you don't want to take it a minute before you go to bed, that you'd probably have better pharmacokinetics at a half an hour or an hour before you go to bed, with a caveat -- I just have to add this.

The FDA is talking about real-world use, and in the real world, we could tell them to take it standing on their head while not thinking of a wolf, and they would still take it at bedtime. It's not clear that the fine points are going to make a difference in practice.

While we're waiting for them to put up the questions -- I am summarizing b.

Dr. Katz?

DR. KATZ: Yes. Just with regard to the

when to take it question. I know you want to talk about 10 milligrams later. But I think one of the points that Dr. Farkas was making when he mentioned taking it at the right time to maximize the effect is that maybe if you take it earlier, that's a way to get more out of the 10 milligrams. And that's just something I think we should keep in the back of our minds when we get to the 10-milligram question, if we're not there already.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: Well, I think, Dr. Katz, you mentioned that you could talk to a family and say, try this for 7 days, and if it doesn't work, either think of another drug or maybe a wrong diagnosis. And the reason I'm concerned about that is that in the real world, people are not going to under polysomnographic studies. So they're going to have to judge themselves, has this medication or has it not helped me?

So for a 10-milligram dose, for example, if there is a secret polysomnogram in the room, we would objectively say, you're being benefitted.

But the patient would say, I don't perceive a difference, and they would move on. So I think that the perception is going to drive whether someone continues or escalates a dose.

DR. KATZ: Right. But the 7 to 10 days, that's sort of a distraction. I only mentioned it to say that there's something about duration in the label, but it's not about how long to take the drug for.

But as far as the perception driving, let's say, a dose increase, I think it's like anything else. If the doctor prescribes 10 milligrams and after a few days, or whatever period of time everyone agrees is appropriate to see if it's working, if it's not doing well, the patient goes back to the doctor, or the doctor says, come back in a week and tell me how it's going. Together, they make a decision that it's not effective at that dose and they're tolerating, so they can go up. I mean, it's like any other treatment that you would start at a lower dose and see how it goes.

So it would be a perception thing. I think

that's right. But it'll be a clinical judgment.

DR. CLANCY: But that's why I'm saying that the timing is critical because if they literally took when they put their head down, as the study indicates, their perception might be different had they taken a half an hour --

DR. KATZ: Absolutely.

DR. CLANCY: -- and actually had a higher level and fell asleep quicker.

DR. KATZ: Absolutely. And I think that's the point, is that if taking it earlier really increases the likelihood that the drug will be effective, that's something we need to hear from you about, and in particular with regard to the 10 milligrams where there's some question, I suppose, as to whether or not that's an effective dose. The subjective data don't look so great perhaps at 10, but if you take it at the right time, the perception of that dose, like perhaps with every other dose, might be very different.

DR. ROSENBERG: But, Dr. Katz, even though it wasn't a specific discussion question, I think

that that's a message the committee is giving, to consider advising taking the drug earlier.

DR. KATZ: Fair enough. Again, we are particularly interested in the question of the 10-milligram dose and how that fits into this.

DR. ROSENBERG: Dr. Farkas?

DR. FARKAS: I participated probably as much or more than Dr. Katz in these questions. But I just wanted to clarify that we were trying to go step by step. So the first question was the efficacy of the higher doses. I guess that -- anyway, they can add more if they want. But we took a look at like the point estimate and if it's a benefit with the higher doses, and we were interested in people's opinion of that for the higher doses.

We've been talking a lot about the 10-milligram. Everybody's very eager to talk about that. But really, for the first question, we wanted to go step by step and in some sense start with the more straightforward, almost, questions -- I'm not saying it's

straightforward -- and then move on to the other. So while we've talked a lot about the 10-milligram dose here, that it wasn't our intention for this question.

DR. ROSENBERG: We'll be talking about the 10-milligram dose shortly, after we vote. Dr. Katz, take a look at the votes. Is that what we intended? I see we've divided into two votes.

DR. KATZ: Yes.

DR. ROSENBERG: Dr. Farkas, is that correct?

DR. FARKAS: Yes. That looks correct.

DR. ROSENBERG: Do we have any further comments before we vote? I don't know, did you have your hand up?

DR. VOAS: No. I'm sorry.

DR. ROSENBERG: Dr. Schwartz?

DR. SCHWARTZ: Sorry to harp on this. But if you think for the sleep onset at the lower dose, that you have a different feeling than the higher dose, and you separated -- I mean, I guess --

(Laughter.)

DR. SCHWARTZ: I'm not sure how to put that.

DR. KATZ: Well, I guess technically -- well, if you thought, for example, that the low dose didn't work for, let's say, question c, let's say sleep onset, I guess technically you would have to vote no to that question because it refers to the dose range.

DR. SCHWARTZ: So that means you think that both --

DR. KATZ: Well, technically, that's the way it's written. As I said, you could break this out into sub-questions and say, the low dose doesn't work for sleep onset, the high dose. Now, Dr. Rosenberg suggested you just consider the indication.

So we need to get a sense from you -- which we may be getting already -- but we need to get a sense about what you think about both doses because both doses are being recommended.

DR. ROSENBERG: Dr. Schwartz, why don't you give us your opinion on that for the record.

DR. SCHWARTZ: For the low dose, I was --

(Brief pause.)

DR. ROSENBERG: Dr. Schwartz, you'll explain that when you explain your vote. So we'll vote first and --

DR. PORTIS: I understand that we're going to do that afterwards. But it would be very clarifying, given the discussion, to hear her thoughts before. Does that --

DR. ROSENBERG: Yes. I agree. I think you should give your thoughts before.

DR. SCHWARTZ: Okay. I guess what I was worried about with the lower dose on sleep onset was that the magnitude of the effect is smaller. It's not consistently replicated. Many of the p values are in the grey zone on one side or the other of .05. And that was on both of the subjective and the objective measure on sleep onset.

So that's why I was -- the question -- that's why I felt differently about the low dose on sleep onset versus the high dose on sleep onset.

DR. GUILLEMINAULT: One of the problems is

we have no data on 15 milligrams for the dose. And that's one of the problems right now. We have 10 and 20, and we are talking about 15, but we have no data.

DR. ROSENBERG: We have plenty of data on elderly patients at 15. We don't have it on the non-elderly at 15.

Dr. Bagiella?

DR. BAGIELLA: I'm a little confused. We are voting on the 20 and 40. We're not voting on 10. Right? We're not voting on 10?

DR. ROSENBERG: Correct. We are not considering 10.

DR. BAGIELLA: We're voting on the range, right, from 15 to 30 or 20 to 40?

DR. DIMOVA: No. I think that we are voting 20 to 40 for the non-elderly and 15 to 30 for the elderly.

DR. KATZ: Yes. That's correct.

DR. DIMOVA: That is my understanding.

DR. KATZ: Right. We're not talking about 10 milligrams -- we're talking about 10 milligrams,

but we're not voting about 10 milligrams.

(Laughter.)

DR. DIMOVA: Perfect. All right.

DR. ROSENBERG: I just want to show you the algorithm, which is in front of you, just so you can see. So we're voting on what you're looking at. We're voting on these doses. We are combining doses. Dr. Schwartz has expressed her opinions on interpreting the results. We don't know how she's going to vote. We don't know how anyone's going to vote.

I think it's time to vote. I think if you could go to the next slide. Folks, you all have the doses in front of you. Okay.

So first vote: "Are these dose ranges effective for the treatment of insomnia characterized by difficulties with sleep onset?" Your thing should be going on and off, and you press the button that you like. And you can keep changing your mind as long as it's blinking on and off. Please everybody vote.

To clarify, we are voting on c. Everybody

press your button again, please. We're voting on c, the question of efficacy for sleep onset.

(Vote taken.)

DR. JOHNSON: I will now read the vote into the record. We have 12 yes, 4 no, and 1 abstain.

DR. ROSENBERG: Now that the vote is complete, we will go around the table and have everyone who voted state their name and vote, and if you want to, you can state the reason why you voted as you did into the record.

Just because I know to go from right left, we'll start with Dr. Kramer -- we'll start with Dr. Cohen.

DR. COHEN: I voted yes.

DR. ROSS: I voted yes.

DR. ROSA: I voted no because of the lower dose.

DR. RIZZO: I voted yes.

DR. ROSENBERG: We have to go back to Dr. Cohen. State your name for the record, and Dr. Johnson reminds me you should state why you voted as you did.

DR. JOHNSON: You don't have to.

DR. ROSENBERG: State your name for the record, which way you voted, and you have the option of stating the reason.

DR. COHEN: Jeffrey A. Cohen. I have a PowerPoint presentation I'm going to put up. No. I voted yes.

(Laughter.)

DR. ROSS: Richard Ross. I voted yes.

DR. ROSA: Roger Rosa. I voted no because of the lower dose.

DR. RIZZO: Matthew Rizzo. I voted yes based on the evidence.

DR. GUILLEMINAULT: Christian Guilleminault. I voted no because of the lowest dose.

DR. CHERVIN: Ron Chervin. I voted yes. I think if we had only seen the data in isolation on sleep onset without maintenance, we would have voted that overall it's yes. And I think it only looks less robust because we have it in juxtaposition with the maintenance data.

DR. BAGIELLA: Emilia Bagiella. I voted

yes.

DR. PORTIS: Natalie Compagni Portis. I voted yes.

DR. HOFFMAN: Richard Hoffman. I voted yes based on the study results.

DR. CLANCY: Robert Clancy. I voted yes.

DR. ROSENBERG: Paul Rosenberg. I voted yes.

DR. VOAS: Bob Voas. I abstained because I don't feel I'm competent to make that judgment.

DR. MIELKE: Michelle Mielke. I voted yes.

DR. TODD: Jason Todd. Yes.

DR. ZIVIN: Justin Zivin. I voted yes because I think that we need more options.

DR. SCHWARTZ: Lisa Schwartz. I voted no, as you heard, because of the low dose.

DR. MORROW: Dan Morrow. I voted no because of the low dose and the ambiguity of the evidence there.

DR. ROSENBERG: I thank everyone for voting and for, where necessary, stating the reason. I think it's very help because we not only give

numbers to the FDA, but we give reasons, and then can take that under advisement. Right, Dr. Katz?

DR. KATZ: (Nods head affirmatively.)

DR. ROSENBERG: Let's move on to question d: "Are these dose ranges effective for the treatment of insomnia characterized by difficulties with sleep maintenance?"

Once again, we are looking at the whole group of dosages, not treating them individually. But it's the doses that are in your handout, in the algorithm, 15 and 30 for elderly, 20 and 40 for non-elderly. We're voting on our opinion about whether they're effective for sleep maintenance. Please go ahead and vote.

(Vote taken.)

DR. JOHNSON: I will now read the vote into the record. We have 16 yes, 0 noes, and 1 abstain.

DR. ROSENBERG: Once again, we'll go around, and state your name and how you voted. Star with Dr. Cohen.

DR. COHEN: Jeffrey Cohen. Yes.

DR. ROSS: Richard Ross. Yes.

DR. ROSA: Roger Rosa. Yes.

DR. RIZZO: Matthew Rizzo. Yes.

DR. GUILLEMINAULT: Guilleminault. Yes.

DR. CHERVIN: Ron Chervin. Yes.

DR. BAGIELLA: Emilia Bagiella. Yes.

DR. PORTIS: Natalie Compagni Portis. Yes.

DR. HOFFMAN: Richard Hoffman. I voted yes based on study results.

DR. CLANCY: Robert Clancy. Yes.

DR. ROSENBERG: Paul Rosenberg. Yes.

DR. VOAS: Bob Voas. Abstain.

DR. MIELKE: Michelle Mielke. Yes.

DR. TODD: Jason Todd. Yes.

DR. ZIVIN: Justin Zivin. Yes.

DR. SCHWARTZ: Lisa Schwartz. Yes.

DR. MORROW: Dan Morrow. Yes.

DR. ROSENBERG: Thanks so much.

Question 2, now we can talk about the 10-milligram dose. "The applicant has submitted data supporting the conclusion that 10 milligrams is an effective dose. If 10 milligrams were the recommended initial dose, labeling would include a

recommendation to increase the dose, if necessary, to achieve efficacy for an individual patient, if safety of higher doses were considered acceptable. Such labeling could reduce side effects and would be consistent with recent labeling changes for zolpidem products."

Question a, and we will discuss these one at a time: "Please discuss the pros and cons of the general approach of starting sleep-aid drugs at the lowest dose with a reasonable effect, even if not the full effect.:

The floor is open. Dr. Chervin?

DR. CHERVIN: I think the pros in terms of safety are obvious. But I want to mention a con, which may not be immediately obvious to people.

But often you don't get an infinite number of chances with patients to treat them, and if you do something for them that's not effective, you can always think, well, I'll see them back and I'll make it more effective then. Sometimes they don't come back. Sometimes you lose their buy-in. And personally, I think there's some argument to be

made for giving them something likely to be effective first off.

DR. ROSENBERG: I'm going to talk second. It's funny, when you put it this way, it's not exactly an equipoise question. It's a little like, when did you stop beating your wife?

Of course we believe in many parts of medicine that we start low and go slow. The question is, how low? How slow? And what are the cons, pros and cons, of the approaches?

I'm a little biased because my patients are so frail and elderly. So you know what I'm going to say. I'm going to say, start low and go slow. In other words, I haven't heard any argument not to start at the lowest possible dose.

I haven't heard any serious disadvantage -- the thing is, you've got to look at the disease. If we were treating pneumonia with an antibiotic and I gave you a choice of a low dose with a 30 percent cure rate and a higher dose with an 80 percent cure rate, even if the higher dose had more adverse events, you would not take the

lower dose. Not in a million years. Different disease.

It does not take anything away from the importance of the problem to say, number one, just because it has an ICD-9 code doesn't make it an actual disease, it's a very heterogeneous group. And I think you have to allow for the possibility that you pick up a lot of efficacy at that lowest dose.

So I haven't heard an argument from anyone, including from the company's modeling, to say, why shouldn't you start low and go slow? My two cents' worth.

Dr. Guilleminault?

DR. GUILLEMINAULT: I believe that the drug company would have a very strict leveling. I don't want my patient to, on his own, decide in the middle of the night that it doesn't work and take a double dose, which they will do very easily.

So I think that there will be the need to really recommend that the physicians see the patient again when prescribing, having very strict

leveling to assess that the patient is responding, if you do that way. Otherwise, you are going to have a certain number of patients who are not going to come back and are going to take double dose in the middle of the night.

DR. ROSENBERG: Dr. Bagiella?

DR. BAGIELLA: Yes. I want to add to what Christian was saying. He said before, and somehow I thought about it, and whether or not in proposing a dose that it might not be fully effective, that should come with a recommendation not to take another dose within, say, 24 hours so that you don't have the side effect of taking a double dose, which would cause even more adverse events.

So if that happens, it should come with a clear label that doses should be taken at least 24 hours. I don't know what a reasonable interval would be, apart.

DR. ROSENBERG: Dr. Mielke?

DR. MIELKE: I guess this is kind of my question as well, as I was thinking about it more in terms of the self-medication. So either with it

they take another dose in the middle of the night, or they drink alcohol or something to that effect that could exaggerate the effects as well, and how to control for that.

The other question, too, is that if you would require them to come in to adjust the dose, how reasonable would that be, and how likely it is the patient actually going to come in. So if any clinicians have -- I'm not a clinician myself. So if there are any comments on that and concerns in that regard, I'd be interested.

DR. ROSENBERG: Dr. Todd, you definitely are a clinician. What do you think?

DR. TODD: I agree in principle with starting with the lowest dose and titrating. But in my experience, a very small percentage of insomnia patients will accept anything less than the maximum dose of any sleeping pill if they don't feel that it's highly effective.

So I think a very high percentage of people would gravitate to higher doses. So if you had a range of 10 to 40, I think you'd have a very small

percentage of patients who would actually take 10 and stay at 10 unless there was a strong recommendation that they shouldn't be prescribing anything higher.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: Well, what I heard from the sponsor just a little bit ago was that when they looked at all their data, that 10 milligrams was not effective.

DR. ROSENBERG: I'd like to say, looking carefully at the sponsor's graphs, I would have to add a comment that I wouldn't say it was ineffective. It just wasn't as effective. And the question is, what's your threshold? What's your statistical significance? I should also add those are still models.

DR. KATZ: Can I -- I'd just reiterate the comment that Dr. Farkas made a while back, which is question a or subpart a is really a generic discussion. I think part b asks the question explicitly whether or not you think 10 milligrams is an effective dose.

So maybe we could just hear everyone, or everyone who wants to comment, on a, which is sort of the generic point, unless you think we're done with that.

DR. ROSENBERG: Do we have further comment on point a? Dr. Bagiella?

DR. BAGIELLA: About what Jason just said, that most patients want to start at the highest dose, in fact, if you look at the presentation -- one of the slides, I think, is slide 42 this morning -- at 3 months on the subjective scale, 42 percent of the patients on placebo responded.

So that seems a huge response rate for placebo. And the max dose, the response rate was 55 percent, which is not a lot higher. So there is a clear perception on the part of the patient that if they're told that the medicine works, they probably believe that. They probably believe that, and it probably works.

So I really don't see the patient pursuing a higher dose if there is enough of an instruction

that the lower dose might work as well.

DR. ROSENBERG: Dr. Schwartz?

DR. SCHWARTZ: As an internist, I think that patients often are very afraid of side effects. And I think it's probably different if you're in a referral center and you get the people who have the worst insomnia. But I think in a primary care setting, many times people are very nervous about medicines and are happy to go slow.

DR. ROSENBERG: Dr. Todd?

DR. TODD: Well, in clinical practice, patients know if there's a higher dose available or not. In this trial, they got what they got and they didn't know what they were getting. It was a blinded trial.

So with Ambien, before the recent changes, I would almost never see a patient who would actually take 5 milligrams of Ambien and stay at 5 milligrams of Ambien. Now that women -- unless you're going against the recommendation -- now that 5 milligrams is the maximum recommended, people now are suddenly doing okay at 5 milligrams. But I

think that's my real-world experience.

In terms of the graph that you mentioned about the very strong placebo effect in terms of daytime function on the ISI, I'm also impressed with that. Honestly, it looks like the best treatment in terms of balancing of efficacy, effectiveness, and side effects, is placebo.

DR. ROSENBERG: Do we have a vote for placebo? We'll make that question 7.

Dr. Ross?

DR. ROSS: Maybe I misread the question, but it seemed to me like the implication of the question was, would we start a patient at a dose which we knew could reasonably be effective even if we weren't expecting the full effect from that dose.

I know in my own clinical experience, oftentimes I'll start a medication at the lowest dose that can possibly be effective and be quite surprised that it really is fine. I'm thinking of trazodone, which is recommended between 50 and 150 for insomnia; and sometimes you start at 25, and lo

and behold, everything is great.

DR. ROSENBERG: And trazodone is not indicated for insomnia.

DR. ROSS: Right. But of course, everybody's -- excuse me.

DR. ROSENBERG: If the committee's okay with this, I'd like to finish question 2 before we take a break. And the reason is, it seems to me -- I know it's making you wait a little while for the break. But if people don't have a strong objection, it happens, I think, that a, b, c, and d kind of all integrate together and we ought to plow through it quickly.

Who is next? Dr. Chervin?

DR. CHERVIN: I just wanted to mention, with regard to a patient who has concerns about side effects, we haven't talked about it much, but most of my patients who have insomnia don't get any medication. They get cognitive behavioral therapy for insomnia. It's six to eight sessions. It is what it says. It's a cognitive component and a behavioral component. It's very effective. There

are nice trials that show, head-to-head to medication, it does as well, sometimes in the long term better. That's always an option for patients who are worried about side effects.

DR. ROSENBERG: CBT is great if only anybody would use it and if only anybody it was available to perform. Just joking -- I have a friend who does a lot of work with depression and CBT. And when I was recommending a new trial, he goes, "Nobody uses it." So it's very clear that the world of drugs on paper is secondary, but in primary care it's often primary.

DR. CHERVIN: Can I just respond for a second? Because we're considering saying, maybe a drug should be used at a low dose to be safer. Maybe people should be advised and try CBT first.

DR. ROSENBERG: Dr. Portis?

DR. PORTIS: Well, I just want to piggyback on that because if we're giving it a low dose because we're concerned about safety, and then we start leaning over into this discussion of, you have to give people something, then I start to get

more than more troubled by that kind of thinking. And we don't have any data to support the low dose.

DR. ROSENBERG: I think these points are well-taken, but they're outside the role that we can take today. It's something we can take back to our practice, but we still have to talk about the drug here.

Any more comments on the general? I'd like to summarize a. I didn't hear anyone say, don't start low and go slow. We haven't yet discussed the specific question of whether 10 is the right low dose to start with. Let's discuss that.

I would suggest that we talk about b and c together, if you don't mind, because I think they go together. "Please discuss whether the applicant has established that 10 milligrams is an effective dose," and, "Please discuss whether 10 milligrams would be an appropriate recommendation as a starting dose, with labeling that suggests increasing the dose for patients in whom 10 milligrams is not effective."

I'm sorry, I'll give my own two cents'

worth. I don't think the applicant has established that 10 milligrams is an effective dose because the applicant didn't intend to. And when we use the word "effective," we mean a definitive trial, and the applicant chose not to do that definitive trial.

What we have is a somewhat unusual situation. Usually it's the FDA, or those of us on ground review committees, who say, don't do all this post hoc analysis. I don't believe it. But in this case, the post hoc analysis that the FDA did, they conclude that 10 milligrams is effective. So I think we need to look at that.

Then the other question is, would it be the right starting dose, with recommendations to go up? I open the floor to comments. Dr. Bagiella?

DR. BAGIELLA: This is a question, really, for the FDA. Would a phase 2 study be sufficient for you to recommend this dose? Or would you require the company to conduct a phase 3 trial in this dose before you put it on the market?

DR. KATZ: We don't really make a

distinction between phase 2, phase 3. Everybody's got their own idiosyncratic definition of what they think those things mean. If it's an adequate and well-controlled trial, that's good enough for us.

So it's called a phase 2 trial. It's small; at least it's small compared to the other so-called phase 3 studies. But in and of itself, that's no bar to relying on it as providing substantial -- or contributing to a finding of substantial evidence of effectiveness, which is what we really have to find. So it doesn't matter what you call it. If it's adequate and well-controlled, we can rely on it.

DR. BAGIELLA: I guess the question then is, is the data that you have seen sufficient for you from just one small trial to put the drug on the market with this dosage, at this dose? Or would you require more?

DR. KATZ: No. Well, again, this is the question we're sort of asking you, although there's other analyses that include other data as well that potentially speak to the effectiveness of the 10.

But no. It's really a question we're asking you. In our view, it could be seen as an adequate and well-controlled trial. The other studies were 3 months; the treatment periods here were 1 month. But that wouldn't rule out our being able to rely on it.

So the answer is, we could rely on this as sufficient for recommending -- or approving and recommending the 10-milligram dose. We could.

DR. ROSENBERG: Please.

DR. GUILLEMINAULT: I think that your question should be changed because you should say, please discuss if 10 milligrams is an effective dose, not the applicant.

DR. KATZ: Yes. That's --

DR. GUILLEMINAULT: The applicant, as you mentioned, never came up with that.

DR. KATZ: Right. We want to know whether or not you think the evidence supports the conclusion that 10 milligrams is an effective dose. It's true we shouldn't couch it in terms of, has the applicant done it? Have we done it. We want

to know what you think, whether or not you think it's an effective dose based on the data you've seen.

DR. ROSENBERG: But I'd like to point out if you look at discussion question c, that instead of yes/no, maybe is a reasonable answer. Question c is saying, if maybe is the answer, is 10 milligrams is maybe effective -- maybe is not usually used in drug indications.

But if 10 milligrams might be effective, would it be a reasonable starting dose? And I personally think that that makes sense. I realize that you could always say -- you can always say, go back and do a phase 3 trial.

My argument is, I think that the higher dose data is pretty strong. We voted on it, and there's some disagreement, but still pretty strong that the higher doses work. When we get to later, I have definite concerns about the dose-response of adverse events.

So to me, the maybe, which is not usually used in drug indications, is a reasonable place to

start. That's because of the disease we're treating, because this is a disease, a problem, where if you have a partly effective dose or a maybe effective dose, I don't see it doing any harm.

Dr. Rosa?

DR. ROSA: Maybe I'll turn professor, given those comment around. If there's a certain base rate of natural doublers in the population, then wouldn't a 10-milligram starter dose be better for people who tend to double up on their doses anyway?

DR. ROSENBERG: Dr. Katz?

DR. KATZ: Yes. I want to just expand or make a comment about what you just said about if the dose maybe is effective, should we think about starting it. I guess it's a question as to whether or not we should or could, say, recommend starting at a dose that we have not been convinced is effective.

But it might be effective, and it's safer, so writing labeling that says, look, in effect, start here; we're not too sure if it works, but

start here. You can always go up. I guess there's an argument to be made to do that.

But I think what we want to hear -- we'd be interested to hear if you think we should do that, too. But one question we absolutely, I think, want an answer to is, do you think that the data establish that 10 milligrams is effective?

It doesn't have to be effective in everybody. It doesn't have to be as effective as other doses. But do the data support the conclusion that it is effective? If you want to talk about, well, we're not sure but we think it should be recommended anyway, that's a separate conversation. But we really, I think, want to know what you think about that first question.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: Well, if the meaningful endpoint is the patient's perception that the medication has helped them -- and as I understand, that's what they care about, not some number that a test shows -- then the answer is clearly no. They said both 10 and 20 did not move the subjective

scores at all.

So from their point of view, 10 is not going to be effective. And then if you look at the objective information, again according to what we just heard, objectively it's not effective, either.

So I find it hard to recommend a dose that both subjectively and objectively is not any different from a placebo.

DR. KATZ: Can I just -- one thing is one of the analyses suggested that in study 6, 10 and 20 didn't show any subjective movement. But you already voted that 20 is an effective dose. So from other data, we presumably believe that 20 does have an effect on subjective measures, and it doesn't necessarily have to show up in every study.

So the fact that 20 wasn't positive on a subjective and 10 wasn't doesn't mean that they are both ineffective. As I say, you've already concluded that 20 is an effective dose, including based on its effect on subjective measures. So I would just point that out.

Again, as far as objective measures, the

study, study 6, as specified in the protocol and as analyzed in the protocol, clearly was positive on sleep efficiency and WASO, objective wake time after sleep onset. So the sponsor has concluded that it's not an effective dose.

But there is evidence that there are statistically significant effects on objective measures. So there's sleep efficiency, which is the primary outcome, WASO; and because there was a carryover effect in the latency to persistent sleep outcome, the sleep latency outcome, on another objective measure, we did at least one other analysis looking at first period data.

There are many things you could do, but one reasonable analysis that we did also shows statistical significance on latency to persistent sleep. So one view of the results of that study is that all the objective measures were positive. So that's what we want to hear you discuss.

DR. ROSENBERG: I don't want to ask people to pull up slides. But in the handout, if you look at page 12, slides 23 and 24 -- which we've seen

already; I just wanted to point people -- point out to it. It's page 12. It's slides 23 and 24. It would be great if we could pull up the slide, except I don't know if I've got the right number. Start with slide 23.

So slide 23, which is LPS and WASO, objective measures, I think those are pretty solid evidence of 10 milligrams' effectiveness on objective measures, and not very different, not terribly different, from the higher doses.

If you look at slide 24 -- next slide, please; thank you -- it's equivocal. It's not that great on subjective measures. But once again, I think we're asking ourselves whether a lower standard for a safer dose is appropriate as a starter dose.

Obviously I'm a little biased. I'll reveal my bias. Yes, I think that a lower standard and a lower starting dose has got to be a safer way to start, regardless of whether people double or don't double.

That's the end of my jabbering. Dr. Farkas?

DR. FARKAS: Thanks. I think that just to address one of the recent things that you said about the standards, we don't think that it's a lower standard. And the way to explain that, I think, is that we have a guidance on how to -- or how much efficacy data that we need. And we describe situations in which you need less than two studies.

So one of those situations would be where you already have established that the drug works, and then you're looking for efficacy, perhaps in a related indication, in this case for a different dose of the drug. It could be in pediatric population or whatnot.

So we have in some sense the one study from the higher dose. And then when you look at the lower dose, if you have an additional positive study, you kind of have that two sources of independent data to make your conclusion. So it isn't lowering the standard.

I think -- Dr. Katz said that before, to the phase 2 study -- that it looked like it was

positive by the prespecified endpoint. So I don't know we're lowering the standard.

The second point, I think we had purposefully, Dr. Unger and I when we were writing these, had these questions, the discussion questions. And I think that d was really critical, a really critical part of this discussion. Let me just pull it up.

So if the 10-milligram dose has not been adequately established as an effective dose, discuss if the sponsor should be required to perform additional studies of the 10-milligram dose. And I think the key thing here is that when we look at studies as positive or negative, we have to know if they were capable of finding an effect if it was there. And small studies are underpowered to find effects that are there. So the 15 and 20 and the other studies were conducted with something like ten times more patients, and they were adequately powered to show if there was an effect.

So we have the phase 2 study, and I think

that the FDA is trying to use all the data that's available, trying to make reasonable conclusions based on the data that we have, not require -- I don't mean to say there's some conclusion here exactly, but not require people to do unnecessary studies for something that we already know.

But on the other hand, it's just really important to consider that a small, underpowered, negative study does not mean the drug does not work. And I think that's what we were really trying to get at.

So I think the real question is we think -- and I think we've already said that we think there's a pretty good chance that in an adequately powered study -- and adequately powered in insomnia means 600 patients or something -- that the 10-milligram dose would get that p value less than .05 for the endpoints that we're talking about.

DR. ROSENBERG: Dr. Unger?

DR. UNGER: I actually had wanted to make a point about the slide that was up there, but I

don't think you need to go back to it. What I was going to say is that our eyes tend to track with the point estimates, naturally. But if you look at the confidence intervals, the amount of overlap is pretty striking. It looks like somebody's going to put the slide back up. Yes, there you go.

So if you pay attention to the confidence intervals, you see things -- I mean, if you pay attention to the point estimates. But if you look at the confidence intervals, you see there's quite a bit of overlap.

DR. ROSENBERG: Dr. Rizzo?

DR. RIZZO: I'll wait till the vote.

DR. ROSENBERG: Dr. Chervin?

DR. CHERVIN: I just would like for clarification, perhaps from Dr. Farkas. So is the FDA going to require then on all trials like this that a sponsor have a large phase 3 trial at a dose that they think would be effective and also at a low dose that they think would not be effective so that they can come back and convince the panel that they've shown that there's not a lower dose that

should still be tested?

DR. KATZ: We do try to get sponsors to fully evaluate a dose range so we can determine if it's important, the lowest effective dose. Sometimes it may not matter that much.

For example, if the doses that are being recommended for approval or that have been studied are clean and there's no particular safety concern, I guess maybe it doesn't matter if half the dose that you want to approve is equally effective if there's no problem at the dose you're ready to approve. But in a situation where you're really concerned about some adverse event and you want to minimize the possibility that patients will experience that adverse event, particularly if that adverse event is something you're very worried about -- in this case, there are things we're worried about -- then we think it's very important to identify a dose that is effective that may not be as effective or as effective in as many people.

But as Dr. Farkas was saying during his formal remarks, the idea is really here, in our

view, to minimize the risk. There may be an irreducible incidence of a bad thing, but we want to do everything we can to avoid it if we can.

That's why in this particular case we are so concerned about identifying a dose that we think really is effective but low enough so that the risk is mitigated to the extent possible. And in that regard, I would just reiterate what Dr. -- well, anyway, he just said it. I don't have to repeat it. But that's the critical thing, identifying the lowest effective dose when there's something you're worried about.

DR. ROSENBERG: Dr. Voas?

DR. VOAS: The current thought here of starting with the lowest level of the dosing to minimize the risk has a good deal of logic to me. For one thing, it offers the possibility of evaluating the risks in addition to evaluating the benefit for the sleep.

The problem is, I'm wondering from this discussion how you progress from having provided this lower dose to deciding that you go to a higher

dose. Is that going to be entirely upon patient satisfaction? Or what kind of a following data collection process do we have to make that decision?

Is it going to be made, for example, because there's no sale of the product because it's ineffective and it isn't satisfying patients? Or will we make the decision based on what the patient says? Or will we collect data about risk and the extent to which this first level produced risk?

I'm wondering, how does this get handled? I mean, we're talking about a phased use. But how is that decision made and by whom is it made?

DR. ROSENBERG: In the interest of time, I'd like to sum up the discussion to this point. I think the committee has not agreed that 10 milligrams is an effective dose, and I think there's a diversity of opinion on it.

Some opinions are definitely no, and some opinions I think are more like maybe -- I guess my opinion is maybe -- but there's some maybes in there. And similarly, whether 10 milligrams would

be an appropriate recommendation as a starting dose.

I'd like to move to question d and then take a break. Keep in mind, we must finish by 5:00. We've got a lot of airplanes to catch. Everyone who's a Washingtonian knows how difficult it is to get to the airports in rush hour. So let's move on.

D: "If 10 milligrams has not been adequately established as an effective dose, please discuss whether the applicant should be required to perform additional efficacy studies of the 10-milligram dose prior to approval."

Dr. Portis?

DR. PORTIS: Well, it seems that we are very concerned about risk. And so I think absolutely those studies should be required. And I wonder, with all of it together, is there something so special about this drug that it is better than anything else that we have available that we're working this hard considering the risks?

I take very literally where it says, "Such

labeling could reduce the side effects and would be consistent with recent labeling for Ambien." And one of our speakers earlier brought up the problems that have come with Ambien. So I don't want us to tend towards getting into those exact same issues because we've worked so hard to approve a drug that has real problems.

DR. ROSENBERG: Dr. Schwartz?

DR. SCHWARTZ: I agree. I guess if this were a terrible cancer that we had no treatment for, I think we'd in a different position. But this drug works in the range of other drugs, so there are a variety of options. And we don't want to make, I think, the same mistake of not knowing.

So I think it would be great to study and know for sure what the balance of benefits and harms are for the 10 milligrams before approval rather than assuming that we know it.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: This drug is different. It is different. The mechanism is very different. From the data that are available, animal data, for

example -- I had the opportunity to review them -- it worked very differently, and it's much more effective. There were a lot on animal data studies comparing what are called the Z drugs to this new drug.

So the answer is yes. It's clearly something different. But it's something new, so that's the issue. When you have something new, you don't know all the side effects. You don't know everything that you would like to know, particularly in humans. I'm not sure that doing another study is going to bring us much more. That's my only concern.

Currently, what Dr. Chervin is mentioning, it's true that if the patient subjectively feels that it's not responding, they will stop. They will stop in 2 days, in 4 days, and they will double the dose or they will go to something else. That's one problem. Well, for ramelteon and all these, we know that that happened in the past, not that long of a past.

So I'm not sure that -- I think that the FDA

agrees even though -- about what I am saying. They are saying that even with a small study, they believe that they have themselves enough information to recommend something. They are not asking for a new study, really, completely. They are hesitating and they are hiding behind us to make the decision.

The thing is, we don't know. We don't know, and subjectively, the data that we have show that the 10-milligram is not going to do really much. That's the only thing that we can conclude.

My inclination is, it's interesting that from the very beginning, there is a proposal to cut the pair in half, to go to 15, where we only have very little data on. But it seems that it showed the hesitancy on both sides, meaning that the 10 milligrams is probably not going to do too much.

So personally, I don't think that a new study is going to bring that much more information, one. Two, yes, it's a completely new drug, and yes, it has the disadvantage of being like that. Yes, it brings a very different mechanism to the

treatment of the problem.

DR. ROSENBERG: Please note that the questions have changed, and Dr. Katz has asked us to change d. Please read d. It's a vote, and I think it's much simpler and more straightforward for us: Should the applicant be required to perform additional efficacy studies of the 10-milligram dose prior to approval?

I think we should complete our discussion on this because we're in the middle of it, vote, and take our break. I'm still going to say what I think. I don't know that you need additional efficacy studies, and I agree with Dr. Guilleminault. There are a couple of reasons; I want to elaborate.

As a trialist, we're talking here about 10 milligrams, a null finding? You're not required in a trial to have two negative control arms. In other words, placebo is generally the negative control arm. You're not required to also have another dose that's a negative control. If you do, it's convenient. It's helpful. It's not required.

The second the is, I don't know you need additional studies prior to approval because if you look at the adverse events; look, there are occasional drugs where the low dose has more adverse events, but 99 percent of the time, adverse events are going to be higher at the higher dose.

So what is the risk of going ahead with the 10-milligram, of allowing the 10-milligram dose? What is the risk that we're going to find new safety problems that we haven't observed?

Let's complete our discussion on this before we vote.

DR. KATZ: Let me just say that you're going to have to explain -- actually, we're going to go around the room after the vote. But it will be extremely important for us, depending on what the vote is, to be able to interpret what the vote means if everybody explains their vote. And after the vote, I can elaborate a little bit more on what I mean by that. But it will be very important for us to have a clear understanding of why people voted either yes or no. Very important for us.

DR. ROSENBERG: Any further discussion before we vote?

(No response.)

DR. ROSENBERG: Let's vote. Wait till you see the lights blinking, and then you can vote while the lights are blinking. The lights are blinking now. You can vote.

(Vote taken.)

DR. JOHNSON: I will now read the votes into the record. We have 5 yes, 11 no, 1 abstain.

DR. KATZ: If I can again hear -- well, it will be critical for us to know why folks voted no in particular. That could be interpreted in a number of ways. It would be very useful for us to know if you voted no because you think that 10 milligrams has already been shown to be effective, or for some other reason.

That is a critical piece of information that we will need to have in order to interpret this vote. So if everybody who voted no could explain or address that particular point, that would be extremely helpful.

DR. ROSENBERG: Just for variety, we'll start with Dr. Morrow.

DR. MORROW: Dan Morrow. I voted no, and mostly because I didn't feel like there's enough evidence that it has efficacy, that the 10-milligram has.

DR. SCHWARTZ: Lisa Schwartz. I voted yes because I thought that it's a new drug and class, and I think that we don't know -- there's a hint that it's effective, but we don't know. And it might have harm in the real world when people are taking all these other drugs, and I think we could learn more about that before people start taking it.

DR. MORROW: Then I should have said yes, actually.

DR. ZIVIN: Justin Zivin. I voted no because the sponsor clearly indicated that 10 milligrams was ineffective.

DR. TODD: Jason Todd. I voted yes. I think that 10 milligrams is likely to be effective. It's effective by objective measures. It looks

just as good as 20 milligrams in the phase 2 study, study 6.

I think it's a very difficult argument for the sponsor to claim that 20 milligrams is effective and 10 milligrams is not, and I do not buy that argument. And I think it's also a very awkward position to recommend 10 milligrams when the sponsor doesn't believe it's effective. So I think we need a trial comparing 10 and 20 milligrams, at a minimum, perhaps even including 5, to clear things up.

DR. MIELKE: Michelle Mielke. I had voted no because I had felt that there was a lack of efficacy at 10 milligrams.

DR. VOAS: Voas. I voted no because I think that it is a safe point to begin the use. And I don't know believe an extra study will help with more information.

DR. ROSENBERG: Paul Rosenberg. I voted no. I agree with Dr. Voas. I see no reason why studies of 10 milligrams cannot be done post-approval. I'm satisfied with the current risk/benefit analysis.

DR. KATZ: Can I ask, meaning that you think that 10 -- there's already sufficient evidence of effectiveness at 10 to start there?

DR. ROSENBERG: I'm convinced that it may be works, and I'm convinced that it is sufficiently safe that it could be used as a starter dose.

DR. CLANCY: Robert Clancy. I voted yes, there should be a trial. I feel like I'm stuck in an odd episode of the Twilight Zone, when the company's arguing their drug doesn't work and the FDA is arguing, yes, it does. So I need a sleeping pill, I think.

(Laughter.)

DR. CLANCY: I'm just uncomfortable to pick up a bottle that says, "Approved by the Food and Drug Administration to be effective," because I don't know we have -- other than one small study, and then when you look at all the patients they say really no efficacy, I think that's too thin to hang our hat on to say that it's an effective dose.

For some patients, that might be their dose and we're deluding them into thinking we're helping

them simply because they have a perception of it. But anyhow, that's my vote.

DR. HOFFMAN: Richard Hoffman, and I voted no because I think that there is some evidence of efficacy for the 10-milligram dose at this point, and that any necessary additional information could be obtained either through postmarketing surveillance or through a phase 4 clinical trial.

DR. PORTIS: I'm Natalie Compagni Portis, and I voted yes because I believe we don't know that there's efficacy at 10 milligrams. And I'm not comfortable with the benefit/risk profile, and I echo Dr. Clancy's comments that I feel like safety is paramount, and to know that it really does have an effect.

DR. BAGIELLA: Emilia Bagiella. I voted no. I think that the evidence from the phase 2 trial is enough to support the dose at 10 milligrams.

DR. CHERVIN: This is Dr. Chervin. I voted no. I don't think we know for certain that the 10 milligrams is effective. For me, it's a choice of what decisions can we make now, not 2 years from

now with more data. What's the best decision now in terms of the cost/benefit ratio? And I don't see that that ratio is any worse, from the data I've seen, than for several other hypnotics that are currently FDA-approved.

DR. GUILLEMINAULT: Christian Guilleminault. I voted no. I don't believe that there is a demonstration of efficacy, subjective efficacy particularly, with the 10-milligram. And I think that the question is wrongly posed. If I was going to ask to redo a study, I would look at a 15-milligram dose and not at 10 with the data available.

DR. RIZZO: I voted no. I was concerned that the sponsor felt the 10-milligram dose was not effective. I was convinced by the FDA analyses. I think that the 10 milligrams is likely to be effective. I'm not sure that there would be much value of doing an additional trial. I think it would be great to start clinically at 10 milligrams; you have the option of seeing whether it's effective in advancing.

My one concern in this no vote and not doing the extra study is having this written in stone that 10 milligrams is effective, and having a third party payor, for example, saying you can't go higher than 10 milligrams because that's established as the effective dose.

DR. ROSA: I voted no, but it's kind of a borderline no, for unformulated reasons.

DR. ROSENBERG: State your name, Dr. Rosa.

DR. ROSA: My name is Roger Rosa. Basically, Dr. Guilleminault's reasoning. I don't have to repeat it again.

DR. ROSS: Yes. I'm Richard Ross. I voted no for very much the same reasons. I haven't been swayed by the evidence for the efficacy of the 10-milligram dose, and I didn't see at this point a reason for additional studies to establish its safety.

DR. COHEN: Jeffrey Cohen. I abstained. Bob Clancy said it much better than I. It seems like the FDA is wanting Merck to pursue the 10-milligram dosing. I have trepidation about the

medication because it's a novel mechanism, and I do worry about side effects. The problem with voting yes is that it's going to delay this, and it's going to have to be a very large study. So I'm caught between the two.

DR. ROSENBERG: I thank everyone. It's time for a break. It is a quarter to 4:00, 3:44. Let's resume at 5 minutes to 4:00, a 10-minute break. Let's get everybody out on time.

(Whereupon, a recess was taken.)

DR. ROSENBERG: In the interest of time -- I was talking with Dr. Katz -- we're going to skip question 3, which was the question of doses of less than 10 milligrams, and that's really based on our discussion of question 2.

Let's move on to question 4: "The applicant has recommended starting doses of 15 milligrams in elderly and 20 milligrams in non-elderly. Is the safety of these doses acceptable?"

Dr. Chervin?

DR. CHERVIN: I think that there are clear safety issues. We are used to using a lot of drugs

already for our patients that have safety issues. I have not seen any evidence that suggests that this drug at these doses is anything worse than what we have come to expect and be careful with.

DR. ROSENBERG: As an Alzheimer's specialist, I can tell you that all the approved drugs for insomnia I think are pretty bad for my patients, and that the only drug I use is trazodone, which is not approved.

I want to ask you, how do you think these adverse events at this dose compare with the current approved drugs, which I'm sure you've used, particularly the Z drugs?

DR. CHERVIN: Well, there are several different adverse events of concern that were brought up. One of them is, for example, the parasomnia. The current drugs that we use, hypnotics, for -- actually at any age -- can induce parasomnias.

So it was not anything new to read that this one may have done -- for example, the man who jumped up and hit his face. Those unfortunately

are risks. They've been publicized by the media a lot. They don't happen that often. I don't think they happen that often in this trial, either.

I don't think that the one case of possible cataplexy, my reading of it, I don't think it really was cataplexy. That gentleman was weak for about 11 hours. Maybe it's a new form of cataplexy that doesn't resemble what we usually see.

But whatever it was -- and who cares, really, what the name of it was -- the issue is what's important to the patient. And I don't see that that was so incapacitating or of such heavy concern that it leaves me very worried.

DR. ROSENBERG: Dr. Clancy?

DR. CLANCY: So my concern was within the somnolence category. If I understood correctly, there's one category where the person just says, I feel tired. I lack energy. And that's okay.

The other category though was, I guess, EDS, excessive daytime sleepiness. But included within that are unexpected periods of irresistible sleep. And that was, I don't remember, 1.1 percent in the

highest group compared to a much smaller number in the placebo.

I guess, first of all, that's not narcolepsy, but it's suggestive of that. But again, if you're driving and unexpectedly have a severe urge to sleep, I think that could be a problem. And if it's 1.1 percent and we're talking about a third of the population having insomnia and some very, very large number of patients consuming the medication, if you do the math on that, that could be a lot of folks.

DR. ROSENBERG: Dr. Portis?

DR. PORTIS: I have to say, with all due respect, that I'm not comfortable approving something because it's no worse than what we have. I think we want something better than what we have.

I think since the numbers are small in what's been studied, we don't know if some of the effects are even larger when this is given to a wider population, a clinical population that will be taking other medications, as people have pointed out.

The other thing that someone mentioned, this is a new action. It's a new class of drug. And we don't have any long-term data on what the effects of orexin antagonists will be. So I think there's a lot of things we don't know, and I think the risks are significant.

DR. ROSENBERG: Dr. Bagiella?

DR. BAGIELLA: I have mainly a question about this, which is, is this question asking us whether or not these doses -- the safety is not acceptable, meaning that they shouldn't be given, or they shouldn't be as a starting dose? So if a patient starts at 10 but we think that a 20-milligram dose has non-acceptable safety, then the patient shouldn't raise the dose or -- I'm kind of unclear about this question.

DR. ROSENBERG: Dr. Katz, you can chime in. But my understanding is we're talking about these doses and whether it's acceptable to give to people.

DR. BAGIELLA: Right.

DR. ROSENBERG: Forget about 10. Forget

about labeling. We're asking the hard-core question, is this acceptable risk or unacceptable risk?

DR. BAGIELLA: Right. So we're being asked -- so if we decide that this dose is not acceptable, it means that it shouldn't be given at any time?

DR. ROSENBERG: Dr. Farkas?

DR. FARKAS: Yes. The question said starting dose, and I really appreciate your question, right, and how -- that could be like a second question because presumably the answer would be different if patients had started on a lower dose and didn't have safety problems and then were increased to the higher dose. But we didn't want to imply that. And so it was more the question of starting everybody at this dose. That would be the recommended starting dose.

DR. KATZ: Right. We want to know whether or not you think it's safe to start people at these doses. That's the question.

DR. ROSENBERG: Dr. Chervin?

DR. CHERVIN: You know, our ultimate aim is to help patients and do it safely. Sleepiness issues are important. I'm very sensitive to the safety issues. A neighbor who was a friend and a very esteemed colleague last Saturday was driving. He drifted three lanes on the highway, crashed into the embankment of a bridge, and died. So it's clearly an important issue.

But I think that we have to compare this drug to what patients are going to use if they don't have this drug. And that's my point about why I think that it is important to look at this versus the safety risks of other medications.

The concern was raised about sleep attacks. We have other drugs that cause them, this essentially falling asleep or irresistible urge to sleep while you're driving. Dopamine agonists, for example, that we use for Parkinson's or are approved for ALS have a recognized risk. We deal with it. We warn patients about it. I don't want it to happen to more patients. On the other hand, it's a cost/benefit analysis for this drug.

I think that the long-term effects that we saw in the 12-month study were pretty decent. I don't think that many new drugs come to this panel or come to the FDA -- I could be wrong -- with data that are longer than a year. And so I was pretty satisfied with them.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: Most of the side effects were in the higher dosage. If we look at the 15-milligram in the elderly and the 20-milligram, they were much lower. And what Dr. Chervin is stating is 100 percent true.

We are talking about sleep. That's the goal. We are not going to avoid sleep in some subjects if we are talking about a hypnotic drug; any type of hypnotics is going to have this type of side effect. What we want is the lowest number of subjects. If we looked at what was presented, these two doses, 15 and 20 milligrams, are reasonable dosages.

DR. ROSENBERG: Dr. Cohen?

DR. COHEN: So a couple of observations.

The first question I asked to Merck was, what is the ideal patient, or what patient is this indicated in? Because there's a hierarchy of prescribing medications, and the patient that this medication initially would be prescribed to, it's fine if everything else doesn't work. But the reality is that family practice and internists will prescribe the majority of this medication. And secondly, things like obstructive sleep apnea will not be diagnosed and patients with that condition will get it. And it is a new mechanism.

In taking care of patients for a number of years, my average elderly patient is on five medications, also self-treating themselves, also supplements. So I have trepidation about being so blasé about the safety. It's worrisome. I agree that sleep is important; I just don't want it to be permanent sleep.

DR. ROSENBERG: Dr. Zivin?

DR. ZIVIN: Suvorexant does not appear to be any more dangerous than benzodiazepines that I'm familiar with, and therefore, I don't think it's an

unacceptable risk.

DR. ROSENBERG: I'd like to point out that the bugaboo of my own practice is benzodiazepines, both their cognitive toxicity and their obvious abuse potential, potential for dependence, dependence in the sense of addiction.

One of the things that I think is favorable about this drug is sure, there's some rebound insomnia. You'd expect that from an effective drug as well as ineffective. But I see no evidence of withdrawal, tolerance, and all the bad things that happen with benzos.

The second thing is, my biggest concern, excessive daytime sleepiness leading to driving problems, is not nearly as impressive in this low dose as in the higher dose. Dr. Guilleminault is right; if you look at that 2.4 centimeters, that means an inch. You're swaying an inch. At the low dose, there were very few folks who swayed more than that inch. It depends on which analysis you're doing. But I think when we're talking about adverse events, we really need to consider the low

and high dose separately.

Dr. Clancy?

DR. CLANCY: I was struck earlier by a comment that Dr. Todd made when he said, well, I'll start off with 5 milligrams of Ambien or zolpidem, but very few patients stay there. Next thing you know, they go to the max dose. So it might be that these introductory doses are okay, but many patients go to the max. Then once you get on that train, you're going to be riding with that train.

The second thing is what we didn't hear about -- we heard about PK and PD studies looking at alcohol co-administered with the study drug, and some representatives from antihistamines and antidepressants. I don't know if it was done or not, but don't you think it would be necessary to have knowledge on, let's say, zolpidem and this drug, that there must be some people that they get one drug from one doctor and another drug -- and they want to use them together. They like the way zolpidem gets them to sleep. They like the way the other one keeps them asleep.

So I recommend if that can be -- has that been addressed? Do we know that, zolpidem versus -- co-administered with --

DR. ROSENBERG: Can the sponsor respond?

DR. HERRING: Joe Herring, clinical neuroscience, Merck. We've not done a direct drug/drug interaction study with zolpidem and suvorexant. It was mentioned that we'd done a DDI study with alcohol, which as you know is a CNS depressant, and we talked about those results earlier.

DR. ROSENBERG: Dr. Todd?

DR. TODD: Dr. Farkas presented some data that seemed to suggest there might be a first night effect, with a stronger effect on driving with the first dose compared to patients who'd been on medication for more than a week. Is the FDA convinced that that's a real effect?

DR. ROSENBERG: Dr. Farkas?

DR. FARKAS: I thought you were asking the panelists. You're asking me if I think that there's a larger effect on -- there's more

impairment on the first day versus later? That's what the data seems to indicate. I guess that I didn't show -- well, I showed a table and -- yes. The simple answer. I think there's more of an effect on the second day versus the ninth.

DR. ROSENBERG: Dr. Katz, can you comment on the difference between finding a safety unacceptable and advising a caution on the label, how you distinguish those?

DR. KATZ: Well, yes. If we think a dose is unacceptable, we wouldn't recommend it in the label. That's not uncommon, particularly if you think that a lower dose is just as effective. Of course, it depends on the situation as to where you draw the line as an unacceptable dose.

It depends on the indication. It depends on what the toxicities are. But I would say, just genetically, if we conclude that a dose is unacceptable, however we conclude that, we wouldn't recommend it.

The other part of the question is, you asked is there a difference between that and determining

that a dose must be used with caution. It is true, we have lots of labels that say use with caution, but, quite frankly, it's hard to know what that means.

Again, just to make it real in this case, and Dr. Farkas explained this, we have labels that say don't drive or operate heavy machinery until the patients feels that they can do it or whatever the language is. But we've already determined that in many cases the patient can't tell. So that's not that helpful, either.

So we're trying to move away from statements that say, use with caution, because, quite frankly, it's more or less meaningless. And the goal again, as Dr. Farkas and I think I have said earlier, our thinking now is really try to minimize the risk. Do whatever you can to identify a dose or conditions of use that would make the risk as unlikely as possible. That's a much better way to go.

DR. ROSENBERG: Dr. Morrow?

DR. MORROW: I think it's hard to draw

strong conclusions from the driving studies because of the sample size and, really, the limited assessment of performance, of driving performance. And I wish we knew more about the effects of these drugs on driving safety.

DR. ROSENBERG: Further comment on the voting question? Dr. Farkas?

DR. FARKAS: I think potentially we wanted to keep things simple and say, is the safety of these doses acceptable? I'm going to check with Dr. Unger here because we were talking about the exact word.

But the regulations do speak to if safety has been established. And I think that might go to your question, Dr. Morrow. So there is a way to answer that if you think there's not enough evidence of efficacy.

DR. ROSENBERG: Further discussion on this topic?

(No response.)

DR. ROSENBERG: If not, we should vote. You see the vote ahead, in front of us. "The applicant

has recommended the following starting doses. Is the safety of these doses acceptable?" Thanks for voting.

(Vote taken.)

DR. JOHNSON: I will now read the vote into the record. We have 13 yes, 3 no, and 1 abstain.

DR. ROSENBERG: We'll go around the room. Once again, we'll start with Dr. Morrow. Please state your name, whether you voted yes or no, and you have the option of stating your reason.

DR. MORROW: My name is Dan Morrow, and I voted yes. And it's kind of a weak yes. I wish we knew more about the safety, but when you look at the evidence for safety, the concerns are more at the higher dose than the lower doses.

DR. SCHWARTZ: Lisa Schwartz. I voted no. The 20 already showed signs of problems with driving, and also these more worrisome things. And the stakes are really high because so many people have insomnia, and they could really pose a danger to themselves and others.

The 15 I guess was a little bit less clear,

but because they were lumped together, so I guess I was just -- with this idea of the suddenness and whether the driving evaluation was really measured enough to mention to really be sure, it just seems like the stakes are pretty high.

DR. ZIVIN: Justin Zivin. I voted yes, for the reasons that I stated during the discussion.

DR. TODD: Jason Todd. I voted no. I think the primary principal is, first do no harm. In this situation, I'm concerned about the possibility of a first night effect where there might be more impairment of driving after the first dose. So I think that these may be reasonable titration doses, but probably not safe enough as starting doses.

DR. MIELKE: Michelle Mielke. I voted yes, based on the evidence and also in comparison to the side effects of the other options out there.

DR. VOAS: Robert Voas. I voted yes, though I have a preference for the 10-milligram as a start. Also, I voted yes because I believe there should be a lower level for the over-65. This group is at greater risk if you appropriately use

exposure data from mileage on the road. They're also a group that is least likely to be able to follow a regimen and more likely to overdose. So I believe that difference is important, and I voted yes.

DR. ROSENBERG: I'm Paul Rosenberg. I voted yes. I think the observed adverse events at these doses is favorable compared to the current approved drugs.

DR. CLANCY: Bob Clancy. I also voted yes. The lower doses have some concerning side effects. In clinical practice, however, I would tell a family, don't take the first dose until Friday night. You don't have to go anywhere Saturday. You don't drive.

So if I have any doubt, I try to start the medication at a time where the patient's not compelled to do dangerous activities. So I think, to that extent, we can wiggle around the concerns for the first few doses.

DR. HOFFMAN: Richard Hoffman, and I also voted yes. I think the drug has some merit. I'm

much more concerned about the high dose. I think a patient medication guide would be helpful with using this drug, and I also think that a 10-milligram dosage would be useful.

DR. PORTIS: Natalie Compagni Portis, and I voted no, given the safety profile as we know it now in the elderly and obese and women, and the fact that most people are taking other medications.

DR. BAGIELLA: I voted yes. I think that there is some evidence that --

DR. ROSENBERG: State your name.

DR. BAGIELLA: Oh, sorry. Emilia Bagiella, and I voted yes. I think that there is some evidence that there might be an increased risk for these doses, but it's not excessive. I don't think that it's excessive.

DR. CHERVIN: This is Ron Chervin, and I voted yes. I think the safety, and especially safety as acceptable in comparison to the benefit, is okay.

DR. GUILLEMINAULT: Christian Guilleminault. I voted yes based on the data on these dosages and

comparative to what the other drugs are doing.

DR. RIZZO: Matt Rizzo. I voted yes. I want to just make a comment that also pertains to the higher doses, that I find the study of driving with just the SDLP to be austere and uninformative. I think there are likely to be a lot of false negatives, particularly where decision-making is concerned.

I also think it's important to assess awareness of impairment and to have appropriate metrics for safety studies. That can be done, and it should be done in the future, but it hasn't been done yet.

DR. ROSA: Roger Rosa. I voted yes. All the comments I would have made have been made already.

DR. ROSS: Richard Ross. I voted yes. I thought that the safety profile of the low dose compared to placebo, I was satisfied with that.

DR. COHEN: Jeffrey Cohen. I abstained again. My point is that I have no problems with the sleep experts, neurologists, whatever, are

seeing patients. What I worry about is family practice, internal medicine, OB/GYN, that people prescribe the medication; the context, they're not really looking at a hierarchy of prescribing and really not adequately assessing for other causes in what's going on with a patient.

DR. ROSENBERG: Thank you. Let's move on to question 5. Question 5, let me read it. It's a little more complicated.

"The applicant has recommended doses up to 30 and 40 milligrams in elderly and non-elderly patients, respectively, who have not responded to lower doses. Is the safety of these doses acceptable if recommended only for patients who do not respond adequately to lower doses?"

I just want to point out there's an if here. This is an if, higher dose only if they haven't responded to lower doses. The sponsor is proposing that the lower doses be the starting dose. Otherwise, it's the same question -- is the safety profile acceptable?

I open the floor to your comments.

Dr. Chervin?

DR. CHERVIN: The question implies also a tolerance issue, that if you start at the lower dose and you don't tolerate it for some reason, then you will never get to the higher dose and then maybe, in net, there'll be added safety. I think that's implied.

DR. ROSENBERG: The sponsor?

DR. MICHELSON: Yes. Just to clarify to that last comment, he's in fact correct. What we've recommended is not just that they don't respond, but also that they have acceptable tolerability at the dose.

DR. ROSENBERG: I'll put my two cents' worth in. I have concerns about this higher dose based largely on the driving and the somnolence results. The somnolence, if you look at the phase 3 trials, somnolence goes up from about .2 percent placebo, .6 -- I might be a little off, but approximately .6 at the low dose, 1.1 at the high dose. That's a pretty significant jump.

The evidence of problems driving, although

it is scattered, looks dose-dependent, and the low dose is clearly less than the high dose, which is clearly less than zopiclone. So it's a question of where your gut feeling is, where you go with this.

My concern, I don't actually think the symmetry analysis is a terribly good statistic. It's deficient conceptually, because I think what we're really talking here is outliers. The hypothesis is that an outlier, a small number of people, have quite a lot of excessive daytime sleepiness or something like it leading to whatever you call it, swaying while you're driving.

If you look carefully at the doses, there's a lot more of these outliers at the high dose than the low dose. And for that reason, I'm concerned about the safety of the high dose.

As a practical matter, speaking of my Alzheimer's practice, it's really difficult to get people off the road. But everyone has that problem in the room who's a clinician. And so, for that reason, I have a lot of concern.

It's those two. It's the excessive daytime

sleepiness, which is a real number. It is the outliers in the driving. Notice that the mean doesn't change, but that there are more outliers.

Dr. Mielke?

DR. MIELKE: Thanks. Just to build on that, I'm in the same boat. I have some concerns about the safety. But I guess my question is, if you start somebody off on a low dose and they're coming back in and they're requesting a higher dose, then if the higher dose isn't available, then you're going to give them another potential sleep drug, or would you try the CBT? Or what would be the next option then? So that factors into the risk/benefit ratio to me.

DR. ROSENBERG: Dr. Zivin?

DR. ZIVIN: If a patient is properly titrated, starting low and working their way up, as we always should do, this drug is acceptably safe, as far as I'm concerned.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: If we are very concerned, we can get data once the drug is on the

market to decide about higher dosage. We don't have a lot of data despite of all these studies. And even the efficacy between the 20-milligram and the 40-milligram, it's higher, but we don't know the cost/benefit ratio very well.

So that's a problem. It's not drastic, the increase in risk, from what the data are, but it could be. The decision could be postponed.

DR. ROSENBERG: Dr. Schwartz?

DR. SCHWARTZ: I think the higher doses already showed a scary signal in the best of circumstances. And I guess I wanted to just say that I think that -- especially because people will naturally just increase them if they're not working. They might not work any better, but they may just get more harm. So the question is the potential for harm, I think, is really substantial.

DR. ROSENBERG: Dr. Todd?

DR. TODD: This recommendation appears to not have really been tested in the trial. Patients weren't titrated in the study, and I don't think there's any convincing data that the higher doses

are more effective than the lower doses. I agree with Dr. Schwartz.

DR. ROSENBERG: Dr. Morrow?

DR. MORROW: I've been hearing a lot about titration, and I'm not a clinician. Are there well-worked-out guidelines for physicians to talk to patients during titration? Do patients have adequate expectations about what may happen in the next week or so? I know it's a little off topic, but just for my education.

DR. ROSENBERG: Sure, I guess so.

(Laughter.)

DR. ROSENBERG: I think in the real world people assume that you will start at a lower dose and perhaps move up. But it's not always explicit, and usually it's a give and take.

I think for many of us, if we have a drug -- there are many drugs where we expect to titrate up, and we tell people we have that expectation. Try this; we might go up. There are other drugs where we would choose not to do that.

Dr. Chervin?

DR. CHERVIN: There were a significant number of patients who had somnolence as opposed to EDS. I thought that the EDS level was smaller. That's the more severe cases or prolonged somnolence.

But I couldn't tell from reading the material, I think that the large numbers who might have been somnolent, that it included some who might have been very mildly somnolent, who might have said, oh, yes, I'm a little bit more sleepy. But you know, Doc, I love this medicine. It's changed my life because I'm sleeping much better.

Do we have any information, or can we ask the sponsor, or does anyone have information on that? What made up that 10 percent or so, I think it was, of patients who were positive for somnolence as a side effect on the higher dose?

DR. ROSENBERG: Can the sponsor comment?

DR. HERRING: Joe Herring, clinical neuroscience, Merck. I can respond to that question.

In the core presentation, we presented the

data that showed the intensity reported by patients for the somnolence AEs. And you're absolutely right. Actually, the majority of patients reported mild to moderate somnolence. I think that's a really critical point that you've raised. Only .6 percent of the patients that reported somnolence had severe somnolence.

DR. GUILLEMINAULT: Repeat, please?

DR. ROSENBERG: Any further discussion?

DR. HERRING: Zero point six percent of the patients who reported somnolence had severe somnolence.

DR. CHERVIN: Are you able to separate out the mild and moderate?

DR. HERRING: I'm sorry. This is the slide that I wanted to show, which shows that for patients on the high dose of suvorexant, 10.7 percent had somnolence, of which .6 percent had severe somnolence. That was 8 cases.

DR. CHERVIN: Can I just finish that thought? You know, if you've ever prescribed amitriptyline, a very commonly-used drug, used for

a long time. I bet those numbers would be a whole lot worse, and yet we do it. We warn patients. We do it very gingerly. We titrate. The FDA hasn't moved to make that unavailable.

DR. ROSENBERG: Dr. Voas?

DR. VOAS: It appears that this kind of decision -- I'm not a physician, obviously -- is going to be made primarily on the patient's report of somnolence or unsatisfaction with the sleeping. But the issues that are of concern with risk relate to suicide ideology and to the driving.

To what extent will the physician be able to, and can we expect the physicians to be able to, probe that and become aware of it to make this decision?

DR. ROSENBERG: I'd like to comment on this because I've used the Cornell Suicide Scale in one study, and it's pretty sensitive. It's going to ask questions that really get to your lowest level of suicidal ideation.

I am not wildly concerned about those numbers, even though there's a little more on the

drug. Compared to the kinds of issues we have with SSRIs -- which are drugs we prescribe like breath mints; they're approved -- it's not that high.

I'm going to bounce the driving question back to you because you are the driving expert. What is your feeling about the magnitude of the driving problems that are reported? I'm not just saying, did they report any. I'm saying, what do you think about what we call the effect size? Is this enough to matter?

DR. VOAS: I think we don't know, frankly, from the data that we have. I'm impressed with the fact that there has been quite a bit of concern by the sponsor on this and that there's been work on it. Unfortunately, it's not an easy task. Those of us in that kind of study depend upon actual crash records and the studies of those, which can be much more convincing.

Our problem, I think, with the data that we have at this point is that one of the major behavioral problems that lead to crashes is inability to divide attention. And there were a

number of studies done, but I don't think we hit that one on the head.

But it is clear to me that there is a risk. Now, you asked for the tradeoff here, how really significant is that. I have to keep in mind that without medicine, the problem of sleep deprivation and sleepiness is already a problem in driving. So we have a certain level of loss that is hard to quantify in that area. So I think we welcome efforts to overcome that.

The feature here is that we do have evidence that it is a feature. What we've found, for example, in surveying patients, we asked, did your physician talk to you about driving? This tends to be particularly with alcohol because that's what we've had in the past. And we get very low response rates. Physicians do not seem to get into that area.

That's the reason for my previous question. It seems to me that there's a real opportunity here and responsibility for the physicians to make clear that beyond whether I feel sleepy or not, there is

a real risk on the road, particularly since we're talking about people taking this continuously, and we know a lot of other things are going on like very heavy drinking, and we're seeing other drugs used such as marijuana coming into the fore. So there's going to be a greater responsibility on the physician, I think, to discuss this.

DR. ROSENBERG: Is there any further discussion? I would like to try to move this to a vote pretty soon. Any other issues? Dr. Portis?

DR. PORTIS: Just what you said made me think of one other comment, that those with more intractable sleep issues are even more likely, I imagine, to have co-occurring other medical issues, psychological issues, and therefore be even less likely to self-assess and self-police. So it makes my concerns grow.

DR. ROSENBERG: It's like at a wedding. If I hear no further objection, I move that we move on to a vote. Anybody else?

(No response.)

DR. ROSENBERG: Let's vote. So you can see

the question in front of us. It refers to the higher doses that we've been talking about, 30 milligrams in the elderly, 40 milligrams in non-elderly. Same question: Is the safety of these doses acceptable? The caveat is that the proposal is that everyone would start at the low dose before going to the high dose. Thanks for voting.

DR. VOAS: There's a second caveat, that the decision-maker says it's safe.

DR. ROSENBERG: There isn't another caveat in the question.

DR. VOAS: Oh, yes. I'm sorry. I didn't mean to interrupt. But there's two caveats. One is that it's not working --

DR. ROSENBERG: Use the microphone.

DR. VOAS: If I understand it properly in this question, there's two caveats. One is that the prescription is not working at the lower dose, and the second dose, that the decision-maker, the physician, determines it's safe to go to the higher dose.

DR. ROSENBERG: You're right, and the

sponsor added that.

All right. Thank you for voting. Your lights are blinking.

(Vote taken.)

DR. JOHNSON: I will now read the vote into the record. We have 7 yes, 8 no, and 2 abstain.

DR. ROSENBERG: Arbitrarily, we'll start again with Dr. Morrow. I ask you to state your name, how you voted. You have the option of stating why you voted that direction. I'd encourage you to give your reasons since this is a very close vote, clearly a split opinion.

DR. MORROW: I voted no. But as we've discussed, I have concerns about especially the somnolence and the driving evidence at the higher doses.

DR. SCHWARTZ: Lisa Schwartz. I voted no because I think that there's enough toxicity in the best case scenario.

DR. ZIVIN: Justin Zivin. I voted yes for the reasons that I stated during the discussion.

DR. TODD: Jason Todd. I voted no. I think

that there's no compelling evidence that the higher doses are more effective, but there is compelling evidence that they're potentially more dangerous.

DR. MIELKE: Michelle Mielke. I abstained. I think, obviously, there's more side effects with the higher dose. My question internally was what this compares to other options out there and what the risk/benefit ratio is compared to that. And personally, I wasn't sure.

DR. VOAS: Bob Voas. I voted yes on the basis that -- taking the argument that it's going to be primarily outliers, but also relying on the requirement on the physician that there be a decision that it's safe.

DR. ROSENBERG: Paul Rosenberg. I voted no based on the driving data. It just passes my test that it seems like there are too many outliers on driving.

DR. CLANCY: Bob Clancy. I voted no. Even though I think that the lower doses are probably safe, I have to assume that many patients are going to graduate up to the higher doses.

But I'm quite frankly still fixated on this 1.1 percent that experienced excessive daytime sleepiness in which there are sort of unannounced, irresistible attacks of sleep. I'm not saying it's narcolepsy, but again, this is within the study period. There's going to be a lot of people taking it for many years. And I just think that again, if you project out the consequences, that there's going to be fatalities from that.

DR. HOFFMAN: Richard Hoffman, and I voted no because of concern about the side effects with the high dose.

DR. PORTIS: Natalie Compagni Portis, and I voted no. I think the risks are substantial and seem to go up with the higher dose.

DR. BAGIELLA: Emilia Bagiella. I voted no because I think that the data doesn't support enough efficacy to counterbalance the increased adverse events with the higher doses.

DR. CHERVIN: Ron Chervin. I voted yes. This was definitely a harder vote for me than the others, but my gut feeling overall was that we're

not seeing anything different in terms of a dose-response on the safety side, anything different than we would see for any of the hypnotics that we're currently using.

I didn't think that the overall rate of bad outcomes -- and we have something like 275,000 nights on drug; we have about 2,000 patients treated with drug versus a thousand in the control, and I was impressed that there were not major safety -- serious adverse events in those trials.

DR. GUILLEMINAULT: I hesitated a long time. I voted yes, faith in my colleague -- maybe wrong faith. The second issue was the 0.1 percent presented by the data on the severe sleepiness. It's about the same range as any other hypnotics.

DR. ROSENBERG: Don't forget to introduce yourself.

DR. RIZZO: Matt Rizzo. Yes, for reasons that Dr. Zivin stated. I think start low, go slow is likely to be effective with monitoring along the way. I also think that the safety profile of this drug is not any worse, and likely to be better,

than drugs that we're already using. And I think it will be important to have postmarketing surveillance of this drug at the different doses that it's administered.

DR. ROSENBERG: Roger Rosa. I voted yes. My data impression is we're moving in the right direction toward fewer overall effects compared to what's used, what's marketed now. And postmarketing survey is strongly encouraged.

DR. ROSS: Yes. Richard Ross. I voted yes. This also was a difficult vote for me. I ultimately voted yes because, thinking of myself as a clinician who would prescribe the lower dose to a patient who came back and wasn't satisfied, I as a clinician, on the basis of all I know of the efficacy and the safety of the high dose of this medication, I would like to have it as an option in certain patients.

DR. COHEN: Jeffrey Cohen. I abstained again. I tend to be very positive towards new therapeutics. I think in this context, it will be wide open in the context that a lot of nurse

practitioners/family practice people will prescribe this as a first line with 15-minute appointments. I don't think there'll be adequate evaluation for titration or follow-up. I also worry about outliers. And I've said before, the geriatric population that's on multiple drugs.

DR. ROSENBERG: Thanks to all. We're done with our votes. We have two discussion items I suggest we try to address briefly.

The first one, question 6: "The agency believes that in some populations, e.g., obese women, patients taking metabolic inhibitors, the 15-milligram dose results in excessive suvorexant exposure. Please discuss if you agree."

Dr. Chervin?

DR. CHERVIN: What I saw is that the area under the curve, the concentrations in the blood, would be possibly high. And then I saw loose correlation with outcomes of area under the curve. But the actual data on adverse outcomes I didn't think is there or else I didn't hear it, that this group is at higher risk for adverse outcomes.

DR. ROSENBERG: Can the sponsor confirm or comment?

DR. MICHELSON: Yes. That's correct. So we showed in particular the adverse event data -- well, for somnolence, which is the only adverse event that's really common in obese women. And there's not evidence that suggests that that particular group, with both obesity and female gender, were at different risk. Essentially, there was no evidence that, in women, that somnolence varied depending on what their BMI was.

DR. ROSENBERG: I'll just put in my two cents' worth. I do think that the clinical outcomes are more convincing than pharmacokinetics here. Certainly, if you look at the numbers, you'd think it had more. But the actual adverse events are not impressively more.

I mean, labels are full of cautions, which this might well go to the label. But the term here is excessive. The implication is that this would be hazardous or unacceptable.

Further discussion on point 6? Dr. Todd?

DR. TODD: I don't really know the answer to the question. But I would observe that the population studied was fairly dramatically lighter than the population that I see. So I don't think we know in really significantly obese patients --

DR. ROSENBERG: Clarify. Lighter weight?

DR. TODD: Yes.

DR. ROSENBERG: Lower BMI?

DR. TODD: Yes.

DR. ROSENBERG: If there's no further comment, I think the committee has a modest amount of caution on this issue but doesn't sound like it's a huge concern. Is that fair enough?

(No response.)

DR. ROSENBERG: All right. Last and not least: "If you deem the safety of suvorexant to be acceptable at some dose" -- some of us have deemed that -- "please discuss whether labeling could be adequate to protect patients who drive and to protect the public. If so, what would need to be included in labeling?"

Dr. Voas, you're the driving expert. We'd

appreciate hearing from you.

DR. VOAS: I think that this is going to be an area that will tend to be emphasized. The White House Office of the National Drug Program has recommended that all the states pass per se laws on drugs. And that is adding a new dimension to the current laws that exist, which date from early in the last century.

The result of this is the issue about the meaning of having a prescription for a drug. And without a prescription, the detection of drugs in the driver is likely to lead to a prosecution.

The per se law, as is being proposed for the states, would have an exception that said that if the offender had a prescription, that would be an absolute bar against being prosecuted under the per se law. However, the current law, which is an impairment law, depends upon the police officer's judgment as to whether the individual's driving is impaired. If it's impaired, they move ahead with the arrest, and it's up to the individual court whether the prescription has a role in that.

I say that just as background to indicate that this is going to become more and more significant. California, for example, actually had in its state legislature a law that would hold the physician responsible if they did not warn their patients about the effect of a drug on driving.

On the other hand, the discussion I hear today is very discouraging in terms of the belief in the effectiveness of warnings to the public. But I think that in the case of a drug like this, where there is clear evidence that there is some impairment, that absolutely it needs to have a warning on the label.

The physician should be urged to warn their patients, and perhaps pharmacists should be also warned to note that when they give the prescription so that this is in place. Because aside from our hope that it will influence the patient's actions, it also may become a legal feature of the risk that the patient is running by using this drug, particularly if it is used in combination with alcohol.

So there's two potential issues. One is the standard machinery, heavy machinery and vehicle warning, and the other is the question of whether it should also be accompanied by an alcohol warning.

Based on the evidence that has been presented by the sponsors, I'd suggest that it didn't need to be. But my own belief is that it should be accompanied by that because, in fact, a combination of the two -- and that's fairly likely -- will put people in a position where they are likely to be stopped and possibly arrested by the police because they are impaired as drivers.

DR. ROSENBERG: Thank you, Dr. Voas.

Dr. Katz?

DR. KATZ: Yes. I think that's the issue we're trying to get at. Again, we think the drug causes somnolence. We know the drug causes somnolence. That might be related to a driving impairment. We think there's evidence of driving impairment, at least at some doses. But again, it's sort of unsatisfying to say, tell your patient

not to drive until they feel like they're able to, when we really no longer believe that they can tell that they're able to.

So we're really looking for some sort of guidance about what we might be able to say in labeling that actually would be informative and helpful and prevent some driving accidents when we're not really sure that patients can tell that they're ready to drive. So you can help in that regard.

DR. ROSENBERG: Dr. Schwartz?

DR. SCHWARTZ: Well, I'm skeptical about the effect that labeling will have; but certainly using more explicit language like, higher doses can be dangerous to you and others because it can impair your driving, and also to say something like, they can cause important problems driving even if you don't feel sleepy because this can happen all of a sudden.

I think making it very explicit about the harm rather than just being, oh, be cautious, or don't do it -- I think it's about being clear about

why you shouldn't do it and why you might hurt yourself or somebody else.

DR. ROSENBERG: Dr. Rizzo?

DR. SCHWARTZ: I'm sorry. One more thing. Sorry. The other thing I wondered about, which isn't what you asked, but could there be a ban on direct-to-consumer advertising, let's say for the first year after the required postmarketing studies, to make sure that there wasn't a lot of people who this was being used as a first line drug, or doses were being -- you know, so that you didn't necessarily create a lot of market demand in this period of uncertainty.

DR. ROSENBERG: We need to be pretty prompt. We've got about 8 minutes left. Let's make sure we're very much to the point.

Sponsor?

DR. SCAMMELL: Tom Scammell, neurologist, Beth Israel Deaconess Medical Center. I'm a sleep specialist, and I study the orexin system in animals and people. And I think one thing that's gotten a little bit lost in the discussion is this

definition of excessive daytime sleepiness. I have to defer to the others at Merck -- I'm a consultant to Merck today. I have to defer to those at Merck exactly what the definition of excessive daytime sleepiness was.

But my impression was that it did not include abrupt transitions into sleep, sudden, unanticipated episodes of sleep attacks. And this whole idea of sleep attacks and narcolepsy is a bit of a misconception. Most people with narcolepsy doze off in the context of feeling sleepy under sedentary conditions, when it would happen to anybody.

So I think the idea of somebody being suddenly stricken with an attack of sleepiness is a little bit of a misconception, and I'm not sure that the data with suvorexant implies that.

DR. ROSENBERG: Time for a couple more brief comments. Dr. Rizzo?

DR. RIZZO: I agree with the comments that Lisa made. I want to also mention that this is a problem that will solve itself soon on account of

car companies developing algorithms to learn how drivers drive, when they make accelerometer exceedances, to learn when a person is impaired.

These are algorithms that have been designed for sleepy drivers. But the problem with drugs is people become sleepy. So I'm confident that with new technology and modern techniques, including black boxes that are becoming cheaper and cheaper, that we'll be able to know in an individual the dose-response relationships of medications.

DR. ROSENBERG: I fully expect my car to cut me off first thing in the morning after three cups of coffee.

Dr. Katz?

DR. KATZ: Yes. Just minor. I take the point about this so-called excessive daytime sleepiness. I certainly don't know what it is, and maybe people are mischaracterizing that all the time.

But the data do show formal driving impairments. Driving studies showed impairment at certain doses. So whether that's related to this

so-called EDS or what it's related to, maybe we don't even know. But there is empirical evidence that there's driving impairment, and I think that's the more important finding.

DR. ROSENBERG: Dr. Morrow?

DR. MORROW: I just wanted to third the point about explicit language, especially for less educated people with lower literacy skills. There's plenty of evidence that those kinds of folks really don't understand even seemingly simple labels very well. So I would focus on protocols for supporting face-to-face provider/patient communication.

DR. ROSENBERG: Dr. Guilleminault?

DR. GUILLEMINAULT: Why not just ask the prescribing physician to see the patient within a week, systemically, like to assess the status?

DR. KATZ: Well, again, a lot of the issue is, how's the prescribing physician going to know whether the patient's fit to drive? They're not going to rely entirely on reports from the patient about how they feel.

To answer, I think your question, Dr. Schwartz, was could there be a ban on driving. Was that the question?

DR. SCHWARTZ: No. On advertising.

DR. KATZ: Oh, advertising.

DR. SCHWARTZ: Direct-to-consumer advertising.

DR. KATZ: Oh, yes. Yes. I don't know. That's something we'd have to think about. I have no idea. It's not our --

DR. SCHWARTZ: But I guess the other thing is also about driving, whether there could be some driving assessments. I don't know.

DR. KATZ: Well, there's a lot of things you can put in labeling. You can say, don't let the patient drive unless you put them in a simulator and they show you that they can drive. Or you can say in the labeling, don't drive while you take this drug.

I don't know that people would follow that or if that's the right thing to do, but there's a lot of things you can do in labeling. Whether

people will follow them is another question.

DR. ROSENBERG: Dr. Katz, do you have your idea of what to put on the label? Because we're basically advising you of some of the specifics.

DR. KATZ: Well, I think we heard some good, very understandable, clear comments. We'll have to think about what to write.

DR. FARKAS: I know we don't have the time right now. Do we have a minute for another question?

DR. ROSENBERG: We have exactly one minute.

DR. FARKAS: One minute. Well, this is maybe a bigger question, but I'll ask it anyway.

So I guess that perhaps in obstructive sleep apnea, there's an evaluation of how sleepy patients are during the day. And this is a clinical test. Physicians do this.

Is there a possibility of that kind of treatment, directing that kind of treatment, in the label for patients who are taking a drug like this?

Adjournment

DR. ROSENBERG: We will now adjourn the

meeting. Panel members, please remember to drop off your name badge at the registration table on your way out so that they may be recycled. Please catch your taxis, shuttles, and buses so that you may be recycled back to your loved ones and home institutions. And thank you for your time.

(Whereupon, at 4:57 p.m., the committee was adjourned.)